

A Randomized Comparison of Initial Hemodynamic Response Between Three Concentrations of Adrenaline in Lignocaine with Submucosal Infiltration in Septorhinoplasty Patients

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ABSTRACT

Objective: To assess the cardiovascular responses induced by different nasal adrenaline-lignocaine mixtures infiltrations protocols for patients undergoing septorhinoplasty under general anesthesia.

Methods: Our prospective investigation enrolled 212 subjects, aged 26-34 yrs, classified as physical status class I by the American Society of Anesthesiologists (ASA), of both sexes and scheduled for septorhinoplasty under general endotracheal anesthesia during the period from January 2010 to December 2012, at the King Hussein Hospital, King Hussein Medical Centre, Amman, Jordan. Patients were divided randomly into three groups. Patients in group A (n=70) received nasal sub mucosal infiltration of 10.2 ml of lignocaine 1% (10 mg/ml) with adrenaline 0.0025% (25 mcg/ml). Subjects in group B (n=72) received 10.2 ml of lignocaine 1% with adrenaline 0.00125% (12.5 mcg mg/ml), while subjects in group C (n=70) received 10.2ml of lignocaine 1% with adrenaline 0.000625% (6.25 mcg/ml). Cardiovascular parameters including heart rate, systolic blood pressure and mean arterial pressure were recorded every half minute during the first 5 minutes after nasal infiltration. Inter-group statistical comparisons were performed using ANCOVA and intra-group statistical comparisons were achieved using ANOVA.

Results: In comparison with baseline readings, heart rate was mostly increased, systolic blood pressure was mostly decreased and mean arterial pressure was mostly reduced significantly ($P<0.05$) at 60 seconds time interval post infiltration in all three groups.

Conclusions: Local nasal sub mucosal infiltration of different adrenaline concentrations containing lignocaine solutions could increase heart rate and reduce mean arterial pressure during the first five minutes after infiltration.

Key words: General anesthesia, Initial Hemodynamic Response, Septorhinoplasty patients

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Introduction

Local infiltration of adrenaline-lignocaine mixtures is used in many types of surgical procedures such as neurosurgery, maxillo-facial, plastic and ENT surgery to reduce surgical field bleeding, maintain clear surgical field, induce

adequate analgesia, produce homeostasis and reduce mucosal congestion.⁽¹⁾ Septorhinoplasty had an increasing interest between otolaryngologists, although in the past it had its limitations due to nasal difficult anatomy and increased vascularity.

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The potency and the margins of safety of adrenaline are debatable nowadays. Local infiltration of adrenaline at vascular regions may produce cardiovascular modifications. Absorbed injection of infiltrated local anesthetic containing adrenaline can produce potential cardiac side effects mainly hypertension, hypotension, tachycardia and arrhythmias.⁽²⁾ These complications can lead to serious adverse effects in susceptible subjects.⁽³⁾ Theoretically, adrenaline can produce hypotension by stimulation of beta2 receptors at lower concentration,⁽¹⁾ with hypotension effects of adrenaline at sub therapeutic concentration. Higher concentration of adrenaline preferentially stimulates alpha and beta1 receptors, thereby manifesting the vasoconstrictor effect.

Adrenaline occupies 80-90% of adrenal medullary endogenous catecholamine's content. It is a strong agonist at both alpha and beta adrenergic receptors. Although both alpha and beta receptors are stimulated, beta2 vasodilator effects are most sensitive. Beta1 effects cause increases in heart rate and systolic pressure. In low dose, vasodilatation in arterioles (beta2) is clear, diastolic pressure may decrease, pulse pressure widens but mean arterial pressure remains stable. At high dose, alpha mediated vasoconstriction occurs and systolic pressure increases further.⁽⁴⁾

Vasoconstriction is accomplished by combining topical with sub mucosal infiltration of local anesthetic containing adrenaline.⁽⁵⁾ Injectable method involves a local anesthetic, usually lignocaine, with adrenaline at different concentrations. Cohen-Kerem, *et al.*⁽⁶⁾ demonstrated when they compared the effects of topical 1/1000 adrenaline vs. injected local anesthetic containing 1/100000 adrenaline that sub mucosal infiltration was associated with increased cardiovascular changes. We think that sub mucosal infiltration of reduced concentration of adrenaline containing local anesthetic would decrease cardiovascular changes with safer surgical conditions. The choice of injection site and the concentrations used are different among our otolaryngologists.

The aim of our investigation was to assess and evaluate the cardiovascular effects produced by various nasal sub mucosal adrenaline infiltrated concentrations mixed with lignocaine 1% during

septorhinoplasty under general endotracheal anesthesia. The objective was to determine the optimum dose of adrenaline to induce protective surgical environment for the surgeon, anesthetist and the patient.

Methods

Our prospective, double-blind and randomized investigation included 216 subjects, of both genders, aged 26-34 yrs, American Society of Anesthesiologists (ASA) and scheduled for septorhinoplasty under general endotracheal anesthesia at the King Hussein Hospital, King Hussein Medical Center, Amman, Jordan, during the period from Jan 2010 to Dec 2012, after obtaining written informed consents from all participants and the approval of our hospital ethics committee. Subjects with hypertension, ischemic heart disease and arrhythmias were excluded from our investigation.

General anesthesia was induced using fentanyl 3 mcg/kg, propofol 2 mg/kg and cisatracurium 0.15mg/kg. Orotracheal intubation was achieved, through which oxygen 30%, nitrous oxide 70% and 2 MAC of sevoflurane were administered until infiltration was done when 2 MAC of halothane and cisatracurium 0.03mg/kg were used to maintain anesthesia with end tidal carbon dioxide pressure around 30-35mmHg. Patients were monitored for vital signs using pulse oxymeter for O₂ saturation, capnogram for end tidal CO₂ and GE health care monitor for heart rate and non invasive blood pressure including systolic blood pressure and mean arterial pressure.

After exclusion of four subjects, 212 subjects were divided randomly using sealed envelopes into three groups. Group A (n=70) patients received nasal sub mucosal infiltration of 10.5ml (of 1mg adrenaline in 40 ml solution=1:40000) (6 dental cartridges of 1.75 ml each) of lignocaine 1% (10mg/ml) mixed with adrenaline 0.0025% (0.025mg (25mcg)/ml). Subjects in group B(n=72) received 10.5ml (of 1mg adrenaline in 80ml solution=1:80000) of lignocaine 1% mixed with adrenaline 0.00125% (0.0125 (12.5mcg mg/ml), while patients in group C (n=70) received 10.5 ml (of 1mg adrenaline in 160 ml solution=1:160000) of lignocaine 1% mixed with adrenaline 0.000625% (0.00625 (6.25mcg)mg/ml). Infiltration was

accomplished during 40-60 seconds by the surgeon 15 minutes after orotracheal intubation and before surgery.

Cardiovascular parameters including heart rate, systolic blood pressure and mean arterial pressure were recorded throughout the intervention every half a minute during the first five minutes after nasal infiltration at the following time intervals: baseline (0 sec), 30 sec, 60 sec, 90 sec, 120 sec, 150 sec, 180 sec, 210 sec, 240 sec, 270 sec and 300 sec. In all patients. Rate pressure product was calculated as heart rate multiplied by systolic blood pressure which is normally 9600 in healthy adult subjects.⁽⁴⁾

Statistics

Inter-group analysis was made using ANCOVA while intra-group analysis was made by ANOVA or Chi-square test. Changes were significant if $P < 0.05$.

Results

There was no significant discrepancy between the three groups in terms of weight (GA:60-70 kg, GB:55-65kg and GC:60-65kg), age (GA:27-34 yrs,GB:26-32 yrs and GC:25-33 yrs), ASA class and gender. $P > 0.05$. (Table I). There were significant difference between the adrenaline concentrations between the three groups ($P < 0.05$). Four subjects were ruled out from our study due to the presence of arrhythmias on induction of anesthesia.

In comparison with baseline recordings, there were significant cardiovascular modifications regarding an increase in heart rate and reduction of mean arterial pressure between group A and group B at a time, and between group B and group C at another time, both at 60 seconds time interval after local infiltration $P < 0.05$.

Regarding mean arterial pressure, baseline readings were 78, 79 and 80mmHg in groups A, B and C, respectively. There was no significant difference regarding baseline MAP between the three groups (> 0.05). The least significant ($P < 0.05$) recording of MAP in all groups at the eleven time intervals analyzed was at 60 seconds time interval after the start of local infiltration, which was 63, 65 and 67 mmHg, respectively.

At 150 seconds time interval, MAP increased to 94mmHg and 85 mmHg in groups A and B, respectively, but at the same interval it decreased to 73mmHg in group C, also significantly

($P < 0.05$). Mean arterial pressure returned almost to baseline recordings at 240 seconds time interval in group A which was 77 mmHg. MAP returned almost to baseline readings at 90,120 and 180 seconds time intervals in group B which were 80, 80 and 79 mmHg, respectively. In group C, MAP did not return to baseline readings but it remained decreased. (Table II). In terms of heart rate, baseline readings were 68, 66 and 64 bpm in groups A, B and C, respectively. There was no significant difference regarding baseline HR between the three groups > 0.05 . The highest significant ($P < 0.05$) recordings of HR at the eleven time intervals analyzed were at 60 seconds time interval after the start of local infiltration, which were 84, 80 and 76 bpm in groups A, B and C, respectively. At 150 seconds time interval, HR began to decrease almost to baseline readings and remained as such, so it was 71, 68 and 65 bpm in groups A, B and C, respectively. (Table III).

Systolic blood pressure also was seen to decrease significantly at 60 sec time interval. It was 98,100 and 102 mmHg in group A, B and C, respectively (Table IV).

The mean decrease in MAP readings was 17.7% and the mean reduction in systolic blood pressure was 12.3% while the mean increase in heart rate was 17.5%, all at 60 sec time interval. There were no arrhythmias in all three groups. Only in group A we found that rate pressure product at 90 seconds time interval more than 9600 (Table V).

Discussion

High vascularity of nose and the difficulty of bleeding control demand the use of Local vasoconstrictors, electrical coagulation and induced hypotension to promote hemostasis in nasal surgery. Subcutaneous local adrenaline infiltration may induce local vasoconstriction by a direct action on alpha-adrenergic receptors enhancing clear surgical field, reducing bleeding and decreasing mucosal congestion.⁽¹⁾ Local infiltration of adrenaline with local anesthetic is used currently on vascular surgical areas to enhance hemostasis. In our study, there were significant cardiovascular modifications after local adrenaline infiltration in all three groups. The cardiovascular actions of adrenaline are dose dependent and various adrenaline doses can

Table I: Subjects demographics. Data is presented as numbers or mean+/-SD

	Group A (0.0025%)	Group B (0.00125%)	Group C (0.000625%)
number	70	72	70
ASA I	70	72	70
Age (yrs)	30.5+/- (4.5)	29+/- (3)	29+/- (4)
Weight(kg)	65+/- (5)	60+/- (5)	62.5+/- (2.5)
Gender			
F	25	22	28
M	45	50	42

Table III: HR (bpm) effects after adrenaline-lignocaine local infiltration (mean)

	Group A	Group B	Group C
Baseline (0 sec)	68	66	64
30 sec	68	66	64
60 sec	84	80	76
90 sec	80	75	70
120 sec	72	69	66
150 sec	71	68	65
180 sec	71	68	65
210 sec	71	68	65
240 sec	71	68	65
270 sec	71	68	65
300 sec	71	68	65

Table V: Diastolic BP readings (mean)

	Group A	Group B	Group C
Baseline (0 sec)	55	57	55
30 sec	56	58	56
60 sec	47	49	49
90 sec	66	59	52
120 sec	65	58	53
150 sec	70	64	52
180 sec	64	56	53
210 sec	60	55	51
240 sec	54	53	50
270 sec	53	51	49
300 sec	51	50	48

Table II: MAP (mmHg) effects after local adrenaline-lignocaine infiltration (mean)

	Group A	Group B	Group C
Baseline (0 sec)	78	79	80
30 sec	78	79	80
60 sec	63	65	67
90 sec	86	80	74
120 sec	85	80	75
150 sec	94	85	73
180 sec	84	79	74
210 sec	80	76	72
240 sec	77	74	71
270 sec	76	73	70
300 sec	75	72	69

Table IV: Systolic blood pressure readings (mean)

	Group A	Group B	Group C
Baseline(0 sec)	113	114	115
30 sec	113	114	115
60 sec	98	100	102
90 sec	121	115	109
120 sec	120	115	110
150 sec	129	120	108
180 sec	119	114	109
210 sec	115	111	107
240 sec	112	109	106
270 sec	111	108	105
300 sec	110	107	104

Table VI: Rate pressure product (mean)

	Group A	Group B	Group C
Baseline (0 sec)	7684	7524	7360
30 sec	7684	7524	7360
60 sec	8232	8000	7752
90 sec	9680	8625	7630
120 sec	8640	7935	7260
150 sec	9159	8160	7020
180 sec	8449	7752	7085
210 sec	8165	7548	6955
240 sec	7952	7412	6890
270 sec	7881	7344	6825
300 sec	7810	7276	6760

stimulate various types of sympathetic receptors.⁽⁷⁾ A rate of 1-2 mcg/min may stimulate beta2 receptors with bronchial and vascular smooth muscle relaxation. A rate of 2-10mcg/min can stimulate beta1 receptors, increasing heart rate. Dose more than 10mg/min may lead to alpha activation with general vasoconstriction.⁽⁸⁾ Systemic absorption of adrenaline can happen after local infiltration but systemic actions of adrenaline are different in different subjects according to blood concentration.

Local anesthetics, except cocaine, have a biphasic action on vascular smooth muscle, at low concentration they induce vasoconstriction and at clinical concentration they induce mild vasodilatation without hypotension.⁽⁹⁾ So, cardiovascular modifications in our investigation were due to adrenaline absorption.

Yang *et al.* demonstrated that the cardiovascular effects of local adrenaline infiltration depend on adrenaline dose, vascularity area, rate of adrenaline systemic absorption and physical condition of the subject.

They showed that adrenaline-lignocaine mixture may lead to temporary and clear hypotension.⁽¹⁾ Nasal site is highly vascularized with fast adrenaline absorption,⁽⁹⁾ for that our cardiovascular effects were recorded starting at 60 seconds time interval in our groups. Beta 2 receptors are very sensitive with induced vasodilatation in the muscles, so MAP was reduced by 60 seconds time interval. Partial stimulation of beta1 receptors had positive chronotropy of the heart. A high heart rate was the baroreceptor reflex to a decreased blood pressure. The MAP came back soon reaching a higher number due to the action of beta1 receptor and activation of alpha receptors. The reduction of MAP in our investigation was less than in Yang *et al.* study (17.7% and 28%, respectively), while the increase in heart rate in our study was 17.5%.⁽¹⁾ Nevertheless, in another study by Yang,⁽⁷⁾ they reported a 20% decrease in MAP and a 15% increase in HR. In a previous study, it was clearly demonstrated that an increased plasma adrenaline concentration occurred during the first 4 minutes after infiltration.⁽¹⁰⁾ Decreased MAP readings signify that cardiovascular modifications of absorbed adrenaline are dose dependent. Adrenaline plasma concentration via a vascular route is significantly less than after surgical stimulation or psychological stress.⁽⁸⁾ General anesthesia decreases the release of endogenous catecholamine, so the modifications in adrenaline blood concentration relative to endogenous adrenaline are low. General anesthesia covered the sympathomimetic action of the total catecholamine in blood. General anesthesia can reduce bleeding, make surgery easier and enhance clarity of surgical field.⁽¹¹⁾

Hypotension after local adrenaline infiltration during the first 5 minutes doesn't need intervention because soon blood concentration of adrenaline will be adequate. Moshaver *et al.* demonstrated that following adrenaline injection, increases in the heart rate of 10.2 and 7.4bpm were noted after one and two minutes in 1/100000 adrenaline concentration compared with 1/200000 adrenaline concentration. Similarly, systolic pressure had an estimated increase of 17.5mmHg more in 1/100000 group compared with 1/200000 group after one minute and the increase of 18.8mmHg after 2min.⁽²⁾ Yang *et al.* found that MAP decreased and HR

increased at 1.5 min time interval in both previous concentrations.⁽⁷⁾

Under general anesthesia, 20% of patients breathing 1.25 MAC of halothane and who receive subcutaneous infiltration of 2mcg/kg of adrenaline will exhibit arrhythmias. These increases to 100% of patients receiving 2.5-3mcg/kg. Patients breathing 1.25 MAC of isoflurane or sevoflurane and who receive infiltration of 2mcg/kg of adrenaline will have 0% arrhythmias. For that there was a protocol for the use of adrenaline infiltration with halothane: Avoid concentrations of adrenaline greater than 1/100000 and avoid a dosage in adults exceeding 10ml of 1/100000 adrenaline in 10 minutes (100mcg) or 30 ml/h (300mcg). Under general anesthesia, at 1.5 MAC, isoflurane produces around 120 bpm with MAP around 60mmHg, sevoflurane produces around stable low or 100bpm with MAP around 60 mmHg but halothane produces MAP around 70mmHg with low heart rate.⁽⁴⁾ When halothane was used, no patient developed arrhythmias when less than 1.8 mcg/kg was used, but with isoflurane, no arrhythmias occurred when less than 5.4 mcg/kg was used.⁽³⁾

There are few limitations in our investigation. Firstly, it was impossible to evaluate these cardiovascular effects with myocardial inhibition due to general anesthesia. Secondly, our cardiovascular parameters follow-up was only for five minutes and thirdly, we did not measure the plasma concentrations of adrenaline. In the contrary and in favor of our study, deep general anesthesia was maintained before infiltration and local adrenaline infiltration was achieved 15 minutes after orotracheal intubation.

The cardiovascular changes noticed after sub mucosal adrenaline infiltration can be prevented using as low concentration as possible. This can prevent more cardiac adverse events in susceptible subjects and safer surgical conditions. Horrigan *et al.* showed that adrenaline injection even in therapeutic doses can induce increased heart rate with arrhythmias in susceptible patients, with the frequency of hemodynamic toxic side effects increasing in a dose dependent manner.⁽³⁾ A significant increase in the plasma catecholamine level was shown after injection with associated cardiovascular changes due to systemic absorption of adrenaline.⁽¹²⁾

Preventing cardiovascular changes is the essential corner in preventing cardiovascular adverse events. Associated hemodynamic changes during 4mg adrenaline/20 ml saline and 1mg adrenaline/20 ml saline, can be controlled in both groups without significant clinical consequences. The rescue medication need to treat hypertension was more in 1mg adrenaline group but within the recommended limits.⁽¹³⁾

A previous study showed that there was a trend towards elevation of blood pressure in the groups using adrenaline 1/2000 and 1/10000 with a greater occurrence of hypertensive peaks but not using 1/50000. The blood pressure elevation was progressive but very slow during the procedure which could be associated with the anesthesia technique.⁽¹⁴⁾

Adrenaline has become popular because it is cheap and available in every hospital. The major difficulty with adrenaline is to establish the dose that provides the best safety and efficacy. There is no standard concentration defined in the medical literature. Furthermore, when applying adrenaline topically, the total amount that is used is hard to establish. Adrenaline concentrations have varied widely in the literature ranging from 1/200000 to 1/50000 for infiltration. The idea that higher concentrations of adrenaline are needed for improved operability has subtly gained strength. This has been due mostly to the protocols used in health care centers with more experience which adopt concentrations for topical use of 1/5000, 1/2000 or 1/1000. Although there has been a world trend to use more concentrated solutions, studies demonstrating improved safety (incidence of systemic effects) with these concentrations, compared to lower concentrations are lacking.⁽¹⁴⁾

At 60 seconds time interval, if we divide the decrease in SBP by the mean duration of adrenaline infiltration (50 sec), the result in group A is 0.3mmHg for each 10 sec of infiltration use, in group B is 0.28mmHg and in group C is 0.26mmHg. If we divide the increase in heart rate by the mean duration of adrenalin infiltration, the result in group A is 0.32bpm for each 10 sec of infiltration use, in group B is 0.28bpm and in group C is 0.24bpm. If we divide the decrease in MAP by the mean duration of adrenaline infiltration (50 sec), the result in group A was 0.3mmHg for each 10 sec of infiltration use, in

group B is 0.28 mmHg and in group C is 0.26mmHg.

In our search in literature, we did find some investigations of adrenaline infiltrations during septorhinoplasty.⁽¹⁵⁾ For that, we related our investigations to nasal surgery, mainly functional endoscopic sinus surgery. To our surprise, we found that males occupied the largest group (almost double) of our study time during the investigation, but at the same time we did not investigate whether gender had an influence on adrenaline infiltration hemodynamics. We hope that we could study this in the future.

Conclusion

Cardiovascular modifications were secondary to absorption of adrenaline-lignocaine solution. Local adrenaline infiltration induces cardiovascular modifications of HR and MAP during septorhinoplasty under general anesthesia during the first five minutes after infiltration. At 60 sec time interval after beginning of infiltration, MAP decreased significantly and HR increased significantly. Adrenaline 0.0025% can assist in good surgical field without significant hemodynamic changes or arrhythmias.

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