Original Article

Effect of intramucosal infiltration of different concentrations of adrenaline on hemodynamics during transsphenoidal surgery

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Abstract

Background and Aims: Neurosurgeons routinely instill vasopressors, with or without local anesthetics, to prepare nasal passages prior to transsphenoidal surgeries. As there is a paucity of data comparing the effect of intramucosal nasal infiltration of different concentrations of adrenaline that is, 1:200,000 and 1:400,000 in patients undergoing transsphenoidal surgery, we conducted this study to evaluate the effect of these two concentrations of adrenaline with 2% lignocaine on hemodynamics as well as bleeding.

Materials and Methods: Fifty-two American Society of Anesthesiologists I/II patients, aged 15-70 years, undergoing transsphenoidal surgery for pituitary or sellar masses were enrolled. Prior to surgical incision, nasal septal mucosa was infiltrated with lignocaine-adrenaline solution, after randomly allocating them to one of the two groups, with patients in Group A receiving intramucosal infiltration using 2% lignocaine with 1:200,000 adrenaline and those in Group B receiving 2% lignocaine with 1:400,000 adrenaline. Following infiltration, hemodynamic parameters were recorded every 1 min for 5 min and thereafter at every 5 min interval.

Results: Fewer patients (3/24 [12.5%]) in Group B had a rise of >50% in systolic blood pressure, from baseline values, after nasal mucosa infiltration as compared with patients in Group A (9/24 [37.5%]). In addition, mean rise in systolic, diastolic and mean arterial pressure was also significantly lower in Group B as compared with Group A.

Conclusion: Adrenaline in a concentration of 1:400,000 added to 2% lignocaine for nasal mucosa infiltration produces less hemodynamic response as compared with adrenaline 1:200,000 added to 2% lignocaine while at the same time providing similar operating conditions.

Key words: Hemodynamic effects, intramucosal infiltration, lignocaine-adrenaline infiltration, transsphenoidal surgery

Introduction

Trans-nasal rhino septal transsphenoidal approach is one of the most frequently used approaches by neurosurgeons for microsurgical excision of the pituitary gland.[1-3] However, this procedure is frequently associated with severe stress responses causing major hemodynamic changes such as alterations in blood pressure (BP), heart rate (HR), and rhythm.[4,5] Furthermore, neurosurgeons routinely instill vasopressors, with or without local anesthetics, to prepare nasal passages prior to the procedure and to reduce surgical site bleeding.[4,6,7] Major disadvantage of this infiltration is the hemodynamic disturbances like hypertension and arrhythmias that ensue following systemic absorption of adrenaline from a highly vascular nasal mucosa.[8,9] Most of the previous clinical evidence suggests that increasing the concentration of adrenaline beyond 5 μg/ml (1:200,000) increases the toxic circulatory side-effects, without effective vasoconstriction.[10] Hence, even 2.5 μg/ml (1:400,000) adrenaline can produce enough local vasoconstriction and adequate local hemostasis by activation of α-receptors at the site of infiltration.[6,10,11]

In the past various techniques, including increasing the depth of anesthesia[12] and infusion of vasodilators,[1] have been used to attenuate stress responses associated with transsphenoidal surgeries. One of the approaches used to attenuate the pressor response to lignocaine-adrenaline infiltration is to reduce the concentration of adrenaline. Dunlevy *et al.*[6] found that 1% lignocaine with adrenaline 1:200,000 or 1:400,000 provided optimal hemostasis, whereas adrenaline 1:800,000 provided significantly less vasoconstriction as shown by skin Doppler.

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On the contrary, Biswas *et al.*[13] concluded that infiltration of 0.5% lignocaine with adrenaline 1:800,000 at the time of raising the craniotomy flap, provided adequate hemostasis without producing any cardiovascular disturbances.

There is a paucity of data comparing the effect of intramucosal nasal infiltration of different concentrations of adrenaline that is, 1:200,000 and 1:400,000 in patients undergoing transsphenoidal surgery. Hence, we decided to conduct this study to evaluate the effect of intramucosal infiltration of these two concentrations of adrenaline with 2% lignocaine on hemodynamics as well as bleeding following surgical incision in patients undergoing transsphenoidal surgery under general anesthesia.

Materials and Methods

Following approval from the Institutional Ethics Committee and after obtaining written, informed consent we conducted this prospective, randomized, and double-blind study. 52 American Society of Anesthesiologists (ASA) I/II patients, aged 15-70 years, scheduled to undergo elective transsphenoidal surgery for pituitary or sellar masses were enrolled in the study. Patients with decreased level of consciousness raised intracranial tension, recurrent pituitary tumor, pituitary apoplexy, any cardiac pathology, severe hypertension, previous nasal surgery and history of allergy to any of the study drugs were excluded from the study.

All patients were kept fasting after midnight and premedicated with oral ranitidine (3 mg/kg) and oral diazepam (0.1 mg/kg) the night before and at 6 a.m. on the day of surgery. In the operation theater, all patients were monitored for HR, electrocardiogram, invasive blood pressure, peripheral oxygen saturation (SpO_2), end-tidal carbon dioxide ($EtCO_2$), Bispectral index (BIS), minimum alveolar concentration (MAC) and train of four (TOF) count. BIS values were recorded only when the signal quality index was at least 90% and electromyography was <50. General anesthesia in all the groups followed a standard anesthetic technique. After preoxygenation with 100% oxygen for 3 min, anesthesia was induced with intravenous (i.v.) morphine 0.1 mg/kg^{-1} and propofol 2 mg/kg^{-1}. Vecuronium bromide 0.1 mg/kg^{-1} was used to facilitate tracheal intubation and anesthesia was maintained with 66% nitrous oxide in oxygen supplemented with isoflurane (1-2%) and intermittent doses of i.v. vecuronium. Posterior pharynx was packed with moist cotton gauze to avoid entry of the surgical bleed into the esophagus and stomach.

Prior to surgical incision, nasal septal mucosa of patients was infiltrated with lignocaine-adrenaline solution using 23 gauge needle and a nasal speculum. For this patients were randomly allocated to one of the two groups. Patients in Group A received intramucosal infiltration using 2% lignocaine with 1:200,000 adrenaline and those in Group B received 2% lignocaine with 1:400,000 adrenaline. Randomization was done by computer generated random numbers using six block randomization number. The drug for infiltration was prepared by a staff nurse not involved in the assessment of outcome parameters and volume of drug infiltrated was determined by the operating surgeon. Care was taken to avoid multiple punctures into the mucosa. When the mucosa was seen to blanch and elevate from the cartilaginous septum, it was deemed to be properly infiltrated. The incision site bleeding was evaluated and graded as "minimal," "mild," "moderate" or "severe" by the surgeon blinded to group assignment and hemodynamic data.

Hemodynamic parameters were recorded by an independent observer blinded to patient group allocation. Baseline data were defined as the mean of three recordings taken at 1 min intervals prior to intramucosal nasal infiltration. Following infiltration, hemodynamic parameters were recorded every 1 min for 5 min and thereafter at every 5 min interval. Peak response to nasal infiltration was defined as the maximum systolic blood pressure (SBP) (measured invasively) within 5 min postinfiltration. BIS value was targeted at 50 ± 10 and TOF count was kept ≤2. At the end of surgery residual neuromuscular blockade was reversed with injection neostigmine 50 μg/kg^{-1} and injection glycopyrrolate 10 μg/kg^{-1}. The patients were extubated and shifted to postanesthesia recovery room after ensuring adequate reversal of neuromuscular blockade and a BIS value of ≥90.

The primary outcome of our study was the number of patients with >50% rise in SBP following nasal mucosa infiltration requiring rescue drug, whereas our secondary outcomes included the incidence of >20% rise in SBP, mean rise in HR, systolic, diastolic and mean arterial pressure (MAP), time of peak rise in SBP and number of patients requiring propofol to control this rise. We also assessed surgical site bleeding and incidence of hypotension or bradycardia following infiltration.

For sample size calculation, we performed a pilot study on 16 patients (8 in each group). The result of the pilot study showed that in Group A, 62% patients had a rise of >50% in SBP after intramucosal infiltration, as compared with 25% in Group B. Based on these results, to detect a reduction in the incidence of rise in SBP of >50% from 62% to 25% at an α of 0.05 and β of 0.2 (power of 80), sample size of 24 patients in each group was required. This sample size calculation was performed with one-tailed, two-proportion

Z-test. Hence, keeping in mind the possibility of dropouts (10%), we recruited 52 patients in our study.

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 15.0 for Windows). Normally distributed data such as age, weight, height were presented as mean ± standard deviation. Skewed data and ordinally distributed data were presented as median ± quartiles (interquartile range), and categorized data was presented as frequency or percentage. Statistical analysis of normally distributed data was done using Student's *t*-test. Skewed data and ordinally distributed data were analyzed using Mann-Whitney U-test. Categorized data was analyzed using Chi-square test and Fisher's exact test, as appropriate. For hemodynamic variables, two-way repeated measure ANOVA was used. Mauchly's sphericity test with Greenhouse-Geisser correction was used to validate repeated measures factor ANOVA. If significant, within group analysis was done using paired *t*-test and between group analyses was done using unpaired *t*-test. $P < 0.05$ was considered as significant.

Results

A total of 88 patients were screened for the study, of which 58 patients were found to be eligible. As 6 patients refused to give consent, eventually a total of 52 patients were included in this study, with 27 patients in Group A and 25 patients in Group B. 2 patients (1 each from Groups A and B) were excluded from the study as BIS electrode got displaced after draping and subsequently did not work. 1 patient (from Group A) was excluded as nasal mucosa was so thin that it could not be infiltrated, and another one (from Group A) was excluded as he had to be induced with injection thiopentone instead of injection propofol. Hence, we analyzed a total of 48 patients (24 patients in each group) [Figure 1].

The two groups were comparable with respect to patients' age, weight, height, gender, ASA status, amount of infiltration received, pituitary pathology, and baseline parameters (BP, HR, BIS index value, $EtCO_2$, and MAC) [Tables 1 and 2].

Significantly fewer patients (3/24 [12.5%]) in Group B had a rise of >50% in SBP, from baseline values, after nasal mucosa infiltration as compared to patients in Group A (9/24 [37.5%]) [Table 3]. On comparing the incidence of >20% rise in SBP from baseline values, we found that in 13 (54.2%) Group B patients, SBP rose to >20%, as compared with 17 (70.8%) patients in Group A [Table 3]. In addition, mean rise in systolic, diastolic and MAP was also significantly lower in Group B as compared with Group A [Table 3]. Though the mean rise in HR was greater in Group A as compared to those in Group B; however, this difference was not statistically significant. Moreover, time to peak SBP rise was also comparable between the two groups.

There was a significant correlation between the percentage rise in SBP and dose of adrenaline infiltrated into the nasal

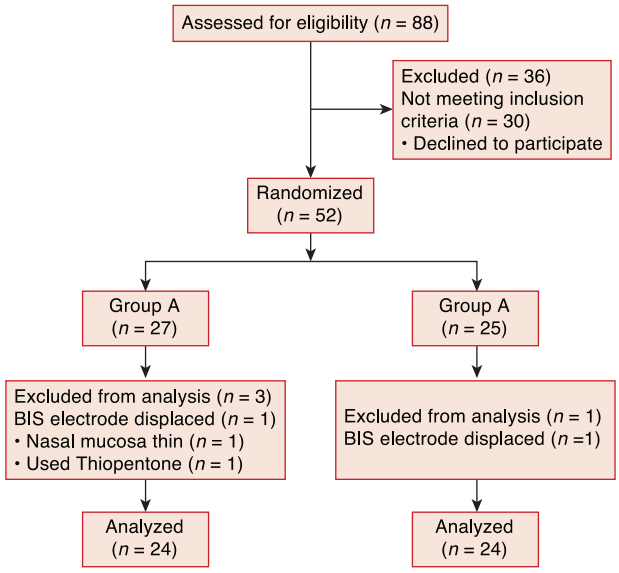

Figure 1: Flow diagram showing study participants

Table 1: Patient characteristics

Demographics	Group A (*n* = 24)	Group B (*n* = 24)	*P* value
Age (years)	42.04±14.08	43.88±13.58	0.648
Weight (kg)	65.54±12.47	70.92±10.08	0.107
Height (cm)	164.71±10.38	166.42±10.44	0.572
ASA status (I/II)	12/12	10/14	0.386
Gender (male/female)	12/12	13/11	0.500
Amount of infiltration (ml)	8.79±2.41	8.71±2.49	0.907
Pituitary pathology			
Nonfunctioning tumor	13	13	
Prolactinoma	5	2	
Acromegaly	3	7	
Cushing	3	2	

Values are expressed as mean ± SD, ASA = American society of anesthesiologists, SD = Standard deviation

Table 2: Baseline hemodynamic parameters

Hemodynamic parameters	Group A (*n* = 24)	Group B (*n* = 24)	*P* value
MAP (mm of Hg)	80.06±12.53	79.75±9.51	0.921
HR (bpm)	71.18±11.45	78.22±16.85	0.097
BIS	48.62±6.61	47.80±5.06	0.632
$EtCO_2$ (mm of Hg)	32.48±3.44	32.94±2.97	0.623
MAC	0.96±0.19	0.97±0.18	0.893

Values are expressed as mean ± SD, MAP = Mean arterial pressure, HR = Heart rate, $EtCO_2$ = End-tidal carbon dioxide, BIS = Bispectral index, MAC = Minimum alveolar concentration, SD = Standard deviation

mucosa, with a 0.96% rise in SBP for every 1 μg increase in adrenaline dose. On comparing the number of patients requiring propofol to control rise in BP, it was found that significantly lower number of patients required rescue propofol in Group B (2/24, [8.3%]), as compared to those in Group A (8/24, [33.3%]) [Table 3]. Further, in Group B, of the 24 patients, 4 had systolic hypotension, and 1 patient had bradycardia. However, none of the patients in Group A had hypotension or bradycardia.

Assessment of postinfiltration surgical bleeding showed that only 1 patient in Group B had moderate bleeding at the incision site postinfiltration, with the rest of the patients having minimal bleeding.

Following infiltration, $EtCO_2$ significantly increased from the baseline in both Groups A and B. However, this difference was statistically insignificant between groups [Table 4]. No significant change in BIS value was noted postinfiltration in Group B, while in Group A it significantly increased from the baseline at 1, 2, and 3 min postinfiltration. Between group analyses also revealed that there was less rise in BIS value in Group B as compared to that in Group A at 2 and 3 min following infiltration [Table 5].

Table 3: Hemodynamic effects of infiltration

Hemodynamic parameters	Group A (n = 24)	Group B (n = 24)	P value
Incidence of >50% rise in SBP	37.5% (9/24)	12.5% (3/24)	0.004*
Incidence of >20% rise in SBP	70.8% (17/24)	54.2% (13/24)	0.371
Mean rise in SBP (mm of Hg)	40.91±26.50	22.51±20.84	0.010*
Mean rise in DBP (mm of Hg)	18.12±12.11	10.34±9.40	0.017*
Mean rise in MAP (mm of Hg)	23.97±16.28	13.00±12.82	0.013*
Mean rise in HR (bpm)	14.86±11.64	12.61±10.51	0.486
Time of peak rise in SBP (min)	1.83±0.63	2.13±0.90	0.201
Patients requiring rescue propofol	8/24	2/24	0.03*

**P < 0.05, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, MAP = Mean arterial pressure, HR = Heart rate*

Table 4: Postinfiltration $EtCO_2$ (mm of Hg)

Time (min)	Group A (n = 24)	Group B (n = 24)	P value
Baseline	32.48±3.44	32.94±2.97	0.623
0	32.96±3.64*	33.71±3.09*	0.446
1	34.62±3.68*	34.92±3.50*	0.780
2	34.75±3.44*	35.17±3.23*	0.668
3	34.29±3.38*	34.87±3.08*	0.535
4	34.04±3.18*	34.33±3.04*	0.747
5	33.92±3.03*	34.25±2.95*	0.702

**Significant increase from baseline within group, $EtCO_2$ = End-tidal carbon dioxide*

Table 5: Postinfiltration bispectral index

Time (min)	Group A (n = 24)	Group B (n = 24)	P value
Baseline	48.62±6.61	47.80±5.06	0.632
0	49.63±6.21	48.38±5.64	0.470
1	52.54±7.32*	49.33±6.15	0.107
2	53.58±7.19*	48.46±5.83	0.009#
3	52.08±8.42*	47.25±4.55	0.017#
4	50.87±7.68	47.79±4.20	0.091
5	49.92±6.60	47.96±4.79	0.246

**Significant increase from baseline within group, #Significant increase between groups*

Discussion

Results of our study reveal that following nasal mucosa infiltration, in Group B significantly lesser number of patients had an SBP rise of >50% from baseline values (severe hypertensive response) as compared with patients in Group A (12.5% vs. 37.5%). Relative risk (RR) of producing severe hypertensive response (>50% rise) in Group A was 3 times greater than in Group B (RR = 3.00, 95% confidence interval: 0.92-9.72). According to the data by Pasternak *et al.*,[14] incidence of severe hypertensive response following intranasal infiltration was 58%, as opposed to our study, wherein the incidence was 37.5% in Group A patients who received similar dose of adrenaline (44 μg vs. 42 μg by Pasternak *et al.*). The lower incidence of severe hypertensive response found in our study could be due to a higher dose of lignocaine (176 mg vs. 42 mg) used by us. Moreover, as Pasternak *et al.*[14] have recorded the data at 2 min intervals, rapid changes in variables and actual peak or trough values may not have been accurately recorded. Further, measurements by Pasternak *et al.*[14] were recorded for a longer duration (15 min) and during that time surgery might have started, thus influencing the results. We ensured that during our observation period there was no surgical or anesthetic stimulation. Similarly, Chadha *et al.*[1] also observed a severe hypertensive response in 85.7% of their patients who received 10-15 ml of 1% lignocaine with 1:200,000 adrenaline; perhaps due to inadequate blood levels of lignocaine required for optimal protection.

Hypertensive response is generally defined as a rise of >20% from baseline. So we did our analysis for this parameter too. Although, as compared with Group A (70.8%), the lesser number of patients in Group B (54.2%) had an SBP rise of >20% from baseline values following nasal mucosa infiltration, this value could not reach statistical significance probably due to inadequate sample size. This shows that the dose required to minimize hypertensive response might be even lesser. Biswas *et al.*[13] showed that adrenaline 1:800,000 was able to minimize blood loss while raising the craniotomy flap. However, the optimal concentration of adrenaline required for nasal mucosa infiltration is not known.

Similar to previous studies,[1,14] we found the absolute and mean rise in systolic, diastolic and MAP postinfiltration to be lower in Group B than in Group A, probably due to lower the concentration of adrenaline used in Group B. Hence, significantly less number of patients required rescue propofol in Group B. The time of peak rise in SBP was at 2 min postinfiltration, which was comparable in both the groups. Hence, probably the maximum effect of adrenaline infiltration occurred at around 2 min that was similar to the observations made in previous studies.[9,15,16]

A few studies have shown the presence of hypotension following nasal mucosa infiltration. Yang *et al.*[17] suggested that many factors could be responsible for contributing to these varied BP effects following local adrenaline infiltration. Firstly, hemodynamic effects of adrenaline are dose-dependent. At low doses, β2 vasodilatory effects predominate, resulting in systemic hypotension, whereas at higher doses α-receptor-mediated vasoconstriction results in hypertension.[18] Yang *et al.*[19] observed that in patients scheduled for endoscopic sinus surgery, intranasal infiltration of both 20 and 40 μg adrenaline-induced significant decline in MAP 1.5 min later. However, at 3 min postinfiltration, there was a significant increase in MAP only in patients receiving 40 μg adrenaline, whereas patients receiving 20 μg adrenaline had a normal MAP by this time. Secondly, anesthesia depth affects MAP response after adrenaline infiltration as found in another study conducted by Yang *et al.*[20] As compared to deeper general anesthesia (BIS 36), lighter anesthesia (BIS 42) led to less decrease in MAP 1.5 min after initiation of adrenaline infiltration with greater rebound in MAP after 3 min. Thirdly, adrenaline induced changes in BP are time-related. Zhao *et al.*[21] observed that systolic, diastolic and MAPs often decreased by 25% of the baseline at 1.5 min after infiltration and then increased to achieve a climax at 3 min postinfiltration. Thus, without appropriate observational time points, one may miss the subtle differences in BP following adrenaline infiltration.

Some previous studies[17,22] have reported the hypotension following the scalp infiltration. This maybe because systemic absorption of adrenaline after infiltration in the scalp, as compared to injection in other locations (such as the nasal mucosa), is probably slow enough to avoid α1 receptor-mediated vasoconstriction, leading to hypotensive response as opposed to hypertensive response. In our study, 4 patients in Group B developed systolic hypotension. It can be presumed that these patients might have achieved such blood concentrations of adrenaline, which led to predominant β2 vasodilatory effects. This could be due to more rapid absorption of adrenaline from the nasal mucosa, or due to deranged pharmacokinetics of adrenaline, or increased sensitivity of β2 receptors in these patients.[13]

Though peak HR increased significantly from the baseline value in both our study groups, this increase was comparable between the two groups. This can be explained by the fact that with increasing blood levels of adrenaline, there is a change in BP response from hypotension (β2 response) to hypertension (α response), whereas HR increases due to β1 response.[18,23] Only 1 patient in Group B showed moderate bleeding at the surgical site postinfiltration. Rest all had minimal bleeding. This shows that adrenaline is equally efficacious in both concentrations that is, 1:200,000 and 1:400,000, for providing local vasoconstriction.

Adrenaline has a big influence on the storage and mobilization of glycogen and fatty acids and the corresponding metabolic pathways. It triggers the adenylate cyclase cascade (or cyclic adenosinmonophosphat cascade), which effects the mobilization of glycogene and triacylglycerines and a general increase of the metabolic rate. Thus, adrenaline, by virtue of its excitatory effects, is known to increase metabolism in the body, leading to increase in CO_2 production and hence $EtCO_2$. In our study also, though $EtCO_2$ significantly increased from baseline values until 5 min postinfiltration in both groups; however, this rise was lesser in Group B when compared with Group A, explained by lesser adrenaline injected. Further, similar to a previous study,[24] there was a significant rise in BIS in Group A patients as compared to those in Group B. Adrenaline is responsible for increases in cardiac output as well as in neural activity, resulting in alertness. Thus, administration of catecholamines can be expected to cause a corresponding change in BIS, due to changes in neurotransmitter levels in the brain, or consequent to increased cardiac output.[24]

There were a few limitations in our study. Firstly, we did not measure the plasma concentrations of catecholamines, particularly adrenaline, and noradrenaline. This was because measurement of these levels was not available in our institute. Secondly, we did not do subgroup analysis based on age, sex, endocrinopathy, and ASA status of the patient. However, the above mentioned factors have been analyzed previously, and they did not differ in hemodynamic response.[14]

Thus, to conclude adrenaline in a concentration of 1:400,000 added to 2% lignocaine for nasal mucosa infiltration produces less hemodynamic response as compared to adrenaline 1:200,000 added to 2% lignocaine, while at the same time providing similar operating conditions.

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