Effect of intravenous lignocaine infusion on the quality of emergence in patients undergoing transsphenoidal resection of pituitary tumors – A prospective, randomized controlled trial

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INTRODUCTION
The anesthetic management of patients undergoing transsphenoidal pituitary surgery (TSS) offers myriad of challenges. The high occurrence of associated cardiovascular disorders such as hypertension, and coronary artery disease makes them susceptible to perioperative cardiac events especially during the periods of stress.[4] It therefore becomes mandatory to maintain hemodynamic stability throughout the operative period. More so being an endoscopic surgery
and any increase in arterial pressure will lead to bleeding in the field thereby hampering visibility.\textsuperscript{[11]}

Emergence from anesthesia is a critical phase in patients of TSS. To ensure smooth emergence various techniques such as deep plane extubation,\textsuperscript{[14]} use of laryngeal mask airway,\textsuperscript{[10]} and short acting drugs such as fentanyl,\textsuperscript{[12]} esmolol,\textsuperscript{[13]} and even lignocaine\textsuperscript{[19]} have been used.

Recently, there has been growing interest in combining local anesthetics with general anesthesia. Lignocaine as an adjuvant to general anesthesia has been shown to have anesthetic sparing effect.\textsuperscript{[2,7]} In addition, due to the cough suppressant properties,\textsuperscript{[3]} a bolus dose of lidocaine is often used to suppress the hemodynamic response at extubation.

Considering these properties of lignocaine and the anesthetic goals of TSSs, we aimed to evaluate the effect of lignocaine on the quality of emergence (QOE) in patients undergoing transsphenoidal resection of pituitary tumors. The effects of lignocaine on intraoperative hemodynamic stability and its sparing effect on volatile anesthetic agents were also evaluated.

**MATERIALS AND METHODS**

The study was conducted at Post Graduate Institute for Medical Education and Research, Chandigarh, after obtaining approval from the Institute’s Ethics Committee (NK/792/MD/1569-70 under Chairmanship of Dr KL Gupta on 20.3.2013) and written informed consent. Fifty ASA 1 and 2 patients, between 18 and 65 years scheduled to undergo transsphenoidal resection of pituitary tumors were enrolled for the study. Patients with reported adverse reactions to lignocaine or other amide local anesthetic agent, those on concurrent treatment with Class 1 anti-arrhythmic drugs, having history of renal or liver insufficiency, heart block or arrhythmias, or undergoing revision surgery for pituitary tumor were excluded from the study.

**Anesthesia protocol**

All the patients received tablet alprazolam 0.25 mg on the night before surgery and tablet ranitidine 150 mg and tablet metoclopramide 10 mg 2 h before surgery as premedication. Patients were fasted according to nil per os guidelines. Intraoperative monitoring included continuous electrocardiography, pulse oximetry, end tidal carbon dioxide, non-invasive and invasive blood pressure, minimum alveolar concentration (MAC), and neuromuscular monitoring. The depth of anesthesia was measured using bispectral index (BIS).

General anesthesia was induced with morphine 0.1 mg/kg, propofol 1% bolus till loss of verbal response to commands and/or a BIS value <40. Vecuronium 0.1 mg/kg was given after checking ventilation to facilitate tracheal intubation. A throat pack was inserted after intubation. Patients were mechanically ventilated to attain normocapnia. Anesthesia was maintained with oxygen-nitrous oxide-desflurane. The concentration of desflurane was titrated to achieve BIS values between 40 and 60. Vecuronium was administered to maintain a TOF count between 1 and 2. Normothermia was attained for all patients. Intravenous diclofenac (2 mg/kg) and ondansetron (4 mg) were administered to all patients 30 min prior end of surgery.

**Study protocol**

Patients were randomized into two groups – lignocaine group \((n = 25)\) and saline group \((n = 25)\) using computer generated number table. The random number was enclosed in sealed opaque envelopes. After shifting the patient into operating room, the sealed envelope was opened by an anesthetic not involved in the study to prepare the drug for infusion according to randomization. Patients assigned to lignocaine group received an intravenous bolus of preservative free lignocaine (1% preparation) of 1.5 mg/kg just before induction of anesthesia with a subsequent continuous infusion of 1.5 mg/kg/h. Patients assigned to the control group received equal volume of saline. The hemodynamic parameters (heart rate [HR] and mean arterial pressure [MAP]), BIS, and MAC values were recorded at predetermined time intervals during preinduction (T1), postinduction (T2), postintubation (for first 5 min) (T3), during infiltration of nasal mucosa with solution of lignocaine and adrenaline (T4), during insertion of Hardy’s self-retaining nasal speculum (T5), at the time of sphenoid bone (T6), and seller ridge dissection (T7), during switching off the anesthetic agents (T8), at the time of extubation and every 5 min after extubation for 30 min.

The aim was to maintain hemodynamic parameters (MAP and HR) within 20% of baseline values. Any deviation from this was classified as hypertension (MAP >20% above baseline) or hypotension (MAP <20% below baseline) and tachycardia (HR >20% above baseline) or bradycardia (HR <40 bpm). Hypertension and/or tachycardia were treated with 1 µg/kg of intravenous fentanyl, if BIS was within the study range. Patients not responding to fentanyl were given esmolol 0.5–1 mg/kg as required. Hypotensive episodes were managed primarily with crystalloids, and 3 mg of i.v. mephentermine, if required. Atropine (0.5 mg) was used for bradycardia associated with hypotension.

All the anesthetic agents including desflurane, nitrous oxide, and drug infusion were stopped after the completion of surgery and packing of the nose. Residual neuromuscular blockade was reversed using neostigmine and glycopyrrolate after return of spontaneous respiratory effort. Tracheal
extubation was performed after the patient responded to verbal commands, demonstrated purposeful movement and had adequate spontaneous respiration.

Time to emergence was defined as the period from switching off of anesthetic agents till tracheal extubation. Maximum MAP and HR attained during this period was recorded as emergence MAP and HR, respectively. ΔMAP (emergence MAP – baseline MAP) and ΔHR (emergence HR – baseline HR) were calculated as the difference between the emergence and baseline parameters. Percentage (%) increase in MAP and HR was also determined.

Patients with percentage increase in MAP ≥20% or those with emergence MAP >120 mmHg were treated with i.v. esmolol 0.5 mg/kg.

Cough during emergence was classified as (none-no cough; mild-single cough; moderate -more than one bout but unsustained that is <5 s cough; severe-sustained, and >5 s bouts of cough). Emergence agitation was divided into four grades (1-calm and cooperative, calm easily arousable and follows command 2-restless, anxious but movements not aggressive, 3-agitated – frequent non purposeful movements; 4-very agitated – aggressive, pulls on tube and catheters; and requires physical restraint).

The four emergence parameters (MAP, HR, cough, and agitation) were abbreviated into an aggregated score for QOE.

Statistical analysis

The statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, version 15.0 for Windows). Mean and medians were calculated for all quantitative variables and for measures of dispersion, standard deviation or standard error were calculated. Normality of data was checked by measures of Kolmogorov–Smirnov tests of normality. For normally distributed data, means of two groups were compared using t-test. For skewed data, Mann–Whitney test was applied. Qualitative or categorical variables were described as frequencies and proportions. Proportions were compared using Chi-square or Fisher’s exact test, whichever was applicable. For comparison of time related variables, repeated measure ANOVA followed by one-way ANOVA was applied. All statistical tests were two-sided and were performed at a significance level of α = 0.05.

Sample size was estimated based on total QOE score of 16. To detect a 4 point increase in the emergence score with the use of lignocaine when compared to placebo with SD of 4, the calculated sample size was 22 per group at a power of 90% and confidence interval of 95%. For possible dropouts, it was decided to include 25 patients per group. The effect size would be one.

RESULTS

A total of 58 patients were screened for eligibility, two did not meet inclusion criteria and two patients refused consent. Out of 50 patients randomized in the study, 23 patients in the lignocaine group and 25 in the saline group completed the study. Two patients in the lignocaine group were excluded from the study. One had severe bradycardia not responding to treatment protocol and hence required cessation of the drug infusion. The other was not extubated at the end of the surgery due to a surgical complication. [Figure 1].

The baseline patient demographics and characteristics are presented in [Table 1]. No difference was found between

| Parameter | Saline group (n=25) | Lignocaine group (n=23) | P value |
|-----------|--------------------|-------------------------|---------|
| Age (years) | 45.3 (±12.7) | 40.4 (±9.9) | 0.14 |
| Sex (male/female) | 10/15 | 12/11 | 0.56 |
| Weight (kg) | 75.1 (±16.4) | 73.3 (±12.7) | 0.68 |
| Asa status (I/II) | 10/15 | 13/10 | 0.25 |
| Hypertension(Y/N) | 9/16 | 4/19 | 0.20 |
| Hypothyroidism(Y/N) | 10/15 | 7/16 | 0.48 |
| Diagnosis (NFPT/Acromegaly/Cushing) | 16/7/2 | 16/6/1 | 0.84 |
| TFT | | | |
| T3 (pg/dl) | 1.22 (±0.53) | 1.13(±0.34) | 0.52 |
| T4 (mcg/dl) | 7.09 (±2.56) | 7.71(±2.3) | 0.39 |
| TSH (mIU/l) | 2.1 (±2.86) | 2.59 (±2.5) | 0.55 |
| Cortisol (nmol/l) | 327.13 (±200.5) | 322.83(±225.8) | 0.94 |
| Baseline MAP | 100.3 (±12.3) | 105(±11.02) | 0.170 |
| Baseline HR | 81.4 (±13.2) | 90.7(±14.8) | 0.026 |
| Baseline BIS | 96.7 (±1.4) | 96.9(±1.79) | 0.678 |

TSH: Thyroid-stimulating hormone, HR: Heart rate, MAP: Mean arterial pressure, BIS: Bispectral index, SD: Standard deviation
the two groups with respect to age, sex, weight, ASA status, diagnosis, comorbid illness, MAP, and BIS values. Although a statistically significant difference was found in the baseline HR in the two groups, it did not seem to be clinically significant [Table 1].

Intraoperatively, the blood pressure was maintained close to the target (within 20% of baseline) more effectively among the lignocaine group as compared to the saline group. Fentanyl was required in only three patients of lignocaine group while eight patients required the drug in saline group to achieve this target. Esmolol which was the second-line antihypertensive agent was also required more frequently in the saline group (five as compared to one). The intraoperative HR and blood pressure were comparable between the two groups. A lower MAC of desflurane was required to maintain adequate depth in lignocaine group as compared to the saline group. This difference was particularly significant at two stages: during insertion of nasal speculum (0.98 ± 0.11 vs. 1.07 ± 0.11; \( P = 0.018 \)) and at the time of sellar ridge dissection (0.99 ± 0.12 vs. 1.07 ± 0.12; \( P = 0.043 \)) [Figure 2].

At emergence, the MAP was higher in the saline group compared to the lignocaine group as was the ΔMAP. Furthermore, the % increase in MAP was higher in the saline group. As a result, esmolol was required less frequently at emergence in the lignocaine group (11 patients [47.8%] in the lignocaine group required the drug while 17 patients [68%] required it in the saline group). The % increase in HR was comparable between the two groups [Table 2].

The QOE score which was an aggregate of emergence MAP, HR, cough, and agitation was however not found to be different between the two groups. Contrary to the

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**Figure 1:** Consort flow chart.

**Figure 2:** Comparison of minimum alveolar concentration of desflurane at predefined intervals in the two groups.
In our study, we used lignocaine to achieve the emergence phenomenon: MAP, HR, severity of cough, and emergence agitation/sedation were developed to objectively assess the QOE. This score formulated by us however needs to be validated using it in a larger group of patients.

DISCUSSION

In this prospective, randomized, double-blind study, we found that intraoperative use of intravenous lignocaine at 1.5 mg/kg/h did not significantly improve the QOE with respect to hemodynamics, incidence of coughing, and emergence agitation. However, lesser number of patients in the lignocaine group required antihypertensive agents in the perioperative period to maintain blood pressure within 20% of baseline. There was a slight decrease in the requirement of volatile anesthetic desflurane. Contrary to the hypothesis, lignocaine did not prolong the time to emergence from anesthesia. The postextubation hemodynamics were found to be comparable between the two groups.

Emergence from anesthesia is a challenge in all patients of neurosurgery as rapid and smooth awakening is desirable. Various studies have been conducted but none with conclusive results. In our study, we used lignocaine to achieve the above mentioned goals considering the following properties of lignocaine: preventing hemodynamic effects by direct cardiac depression and peripheral vasodilation, decreasing CMRO2 and increasing cerebral vascular resistance thereby decreasing ICP, and suppression of cough reflex.

Multiple studies have been conducted to assess the QOE using parameters such as blood pressure, HR, severity of cough, emergence agitation, and respiratory complications such as bronchospasm, laryngospasm, desaturation, and emergence time. However, no aggregated score using two or more of these parameters has ever been created or validated. An aggregated score incorporating various parameters of emergence phenomenon: MAP, HR, severity of cough, and emergence agitation/sedation were developed to objectively assess the QOE. This score formulated by us however needs to be validated using it in a larger group of patients.

It was found that the QOE was not different in patients receiving lignocaine as compared to those given saline. So far, the effect of lidocaine has been evaluated individually on the hemodynamics, cough response, and emergence agitation and there have been conflicting reports on its efficacy. In a previous study conducted by Lee et al., to compare the effect of lignocaine (1.5 mg/kg) with remifentanil (effect site concentration 2 ng/ml) on the emergence response, it was found that remifentanil group had lesser incidence and severity of cough as compared to patients of lignocaine group. Furthermore, the MAP and HR were significantly lower in the remifentanil group than lignocaine group. Another study conducted by Sadegi et al. found that alfentanil decreased airway-circulatory reflexes during emergence from anesthesia better than lignocaine.

Looking at individual parameters at emergence, it was found that the percentage increase in MAP was higher in the saline group. Postextubation parameters were comparable between the two groups [Table 3].

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| Table 2: Comparison of the hemodynamic parameters during emergence between the two studied groups. Data expressed as mean (SD). |
|-------------------------|-------------------------|-------------------------|
| Parameter               | Saline group (n=25)     | Lignocaine group (n=23)  | P value |
| Baseline MAP (mmHg)     | 100.3 (±12.3)           | 105 (±11)                | 0.17    |
| Emergence MAP (mmHg)    | 121.8 (±15.1)           | 119.4 (±16.3)            | 0.61    |
| ∆MAP (mmHg)             | 22.4 (±16.6)            | 15 (±12.8)               | 0.09    |
| Percentage increase in MAP (%) | 27.2 (±19.5)             | 17.2 (±12.2)         | 0.06    |
| Baseline HR (bpm)       | 81.4 (±13.3)            | 90.78 (±14.8)            | 0.02    |
| Emergence HR (bpm)      | 104.1 (±18.6)           | 108.5 (±14.9)            | NA      |
| ∆HR (bpm)               | 23.5 (±16.7)            | 22.3 (±13.7)             | NA      |
| Percentage increase in HR (%) | 30.7 (±23.5)             | 26.75 (±17.3)        | 0.51    |

HR: Heart rate, MAP: Mean arterial pressure, SD: Standard deviation

| Table 3: Comparison of quality of emergence score between the two groups. |
|-------------------------|-------------------------|-------------------------|
| Parameter               | Saline group (n=25)     | Lignocaine group (n=23)  | P value |
| MAP                     | 3 (2–3)                 | 3 (2–4)                 | 0.066   |
| HR                      | 2 (1–3)                 | 2 (1–3)                 | 0.974   |
| Cough                   | 3 (2–4)                 | 3 (2–4)                 | 0.744   |
| Agitation               | 4 (4–4)                 | 4 (4–4)                 | 0.615   |
| QOE score               | 11 (10–13)              | 12 (11–13)              | 0.294   |

QOE: Quality of emergence, HR: Heart rate, MAP: Mean arterial pressure
Similarly, there was no difference in emergence agitation in between the two groups in the present study. There are studies which have shown that intravenous lidocaine does not reduce emergence agitation. Again this can be attributed to the shorter duration of surgery and lesser dose of lidocaine used in the present study than what is required to reduce the incidence of emergence agitation.

Therefore, despite resulting in reduced blood pressure, lidocaine could not holistically contribute to each parameter measuring quality of extubation encompassing hemodynamics, cough response, and emergence agitation in summation.

In conflicting reports by Mraovic et al. and Altermatt et al.,[2,6-8] the former found no delay in time to emergence from anesthesia while the latter Altermatt et al. did report an increase in time to emergence in patients receiving lidocaine. Our study results were consistent with those of Mraovic et al. in that we too found no delay in emergence times in patients receiving lidocaine. The short duration of surgery (lasting <2 h), the use of ultra-short acting agent desflurane for maintenance along with a lower dose of lidocaine could have contributed to the favorable recovery times achieved in our patients.

Intraoperatively, MAP was maintained within 20% of baseline more effectively in patients of lignocaine group with lesser requirement of both fentanyl and esmolol. This difference was prominent at certain points of intense stimulation during surgery like at the time of adrenaline infiltration and insertion of nasal speculum. This is consistent with a study by Hans et al. in which it was found that intraoperative lignocaine did decrease the hemodynamic response to surgery, but did so only in the presence of a painful stimulus indicating a anti nociceptive action rather than hypnotic. The HRs intraoperatively were however similar between the two groups. Although the previous studies have found lignocaine to have sparing effect on both inhalational and intravenous anesthetics, the same result could not be reproduced in our study. Lignocaine had only little if any sparing effect on desflurane which could be due to short duration of surgery and lower dose of lignocaine used in our study thereby preventing adequate plasma levels to be achieved.

CONCLUSION

Our study states that 1.5 mg/kg/h of intraoperative lignocaine infusion did not significantly improve the QOE with respect to hemodynamics, cough, and emergence agitation in patients undergoing transsphenoidal resection of pituitary tumors. Further studies with larger sample size and increasing doses of lignocaine with monitoring of plasma lignocaine levels are required to definitely conclude its role in blunting the airway-circulatory responses at the time of extubation. Using other short acting agents such as opioids, beta-blockers in addition to lignocaine may also improve the outcome as compared to either agent alone.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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