The Effects of Clonidine Premedication and Scalp Infiltration of Lidocaine on Hemodynamic Responses to Laryngoscopy and Skull Pin Head-Holder Insertion During Skull Base Procedures

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ABSTRACT

This study was designed to determine if oral clonidine or lidocaine, injected into the scalp before head-holder (H-H) insertion, would attenuate the hemodynamic effects associated with intubation and H-H placement. Thirty-four patients undergoing skull base procedures were randomized to four groups. Group 1 received clonidine 5 mcg/kg po before surgery with 10 to 15 ml of 1% lidocaine infiltrated at pin insertion sites; Group 2 received clonidine with saline infiltration; Group 3 received a placebo preoperatively and had lidocaine infiltrated at pin sites; and Group 4 received a placebo with saline infiltrated. All patients had a standard anesthetic titrated to a 10 to 14 Hz EEG endpoint during laryngoscopy and H-H placement. Mean arterial pressure (MAP) was similar between groups during intubation, but heart rate (HR) increased in patients who did not receive clonidine. H-H application increased HR and MAP in Group 4. HR also increased after H-H placement in patients who received oral clonidine, while patients receiving scalp lidocaine or both clonidine and scalp lidocaine had little change in either value. Clonidine attenuated HR increases after laryngoscopy but not after H-H placement. Lidocaine injected at the pin sites reduced HR, and MAP increased after H-H insertion. The combination of oral clonidine and scalp lidocaine blunted hemodynamic responses to both intubation and H-H placement.

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Clonidine is an antihypertensive agent that reduces sympathetic outflow via α_2 -adrenergic receptor stimulation.¹⁻² Clonidine also decreases anesthetic requirements and blunts the hemodynamic response to endotracheal intubation in patients undergoing major cardiovascular procedures, making this agent a useful adjunct for maintaining hemodynamic stability during noxious stimuli.³⁻⁵

The skull-pin head holder (H-H), used to secure the head of patients during neurosurgical procedures, produces an intense nociceptive stimulus when applied and results in abrupt increases in blood pressure and intracranial pressure (ICP) in patients under general anesthesia.⁶⁻⁷ Different anesthetic and pharmacologic techniques, including lidocaine, antihypertensives, and deepening of anesthesia, have been proposed to blunt this deleterious effect.⁷⁻⁸ Lidocaine, administered subcutaneously at the head-holder pin sites, was more effective in preventing the blood pressure response to skull-pin H-H than was deepening the level of anesthesia.⁸⁻⁹ This method was also as effective as an anesthetic bolus technique utilizing alfentanil.¹⁰

Clonidine is available in oral and transdermal forms in the United States. Using an intravenous clonidine preparation available in Europe, Favre et al.¹¹ tried to attenuate the hemodynamic response to H-H placement but had mixed results. Another study using oral clonidine demonstrated significant reductions in mean arterial pressure (MAP) after pin head-holder (H-H) insertion.¹² In the present study we compared, under stable anesthetic conditions, the effects of oral clonidine or lidocaine injection at the pin application site, alone or in combination, to determine which produced the most stable hemodynamic conditions during laryngoscopy and pin H-H placement.

MATERIALS AND METHODS

Patient Population

After Institutional Review Board approval from the participating institutions and informed written consent, 34 patients scheduled for major intracranial procedures were studied (ASA physical status I-III; age range, 18 to 65 years). Patients were excluded if they had a history of hemodynamic instability or bradycardia, had evidence of hematologic, renal, or liver disease; or were receiving beta blockers, tricyclic antidepressants, or monoamine oxidase inhibitors. Patients were randomly assigned to one of four treatment groups: *Group 1* (n = 7) was given clonidine (5 mcg/kg orally) 90 minutes before surgery and 10 to 15 ml of 1% lidocaine subcutaneously infiltrated at the pin insertion sites approximately 3 minutes before insertion of the skull-pin H-H; *Group 2* (n = 7) was given clonidine (5 mcg/kg orally) 90 minutes before surgery and 10 to 15 ml of saline infiltrated subcutaneously at the pin sites 3 minutes before H-H insertion; *Group 3* (n = 9) was given an oral placebo 90 minutes before surgery and 10 to 15 ml of 1% lidocaine infiltrated subcutaneously at the pin sites 3 minutes before H-H insertion; and *Group 4* (n = 11) was given a placebo orally 90 minutes before surgery and 10 to 15 ml of saline for subcutaneous infiltration 3 minutes before H-H insertion. All the medications were prepared by the pharmacy, and the investigators were unaware of the identity of the study drugs. The clonidine or placebo was given before the patient arrived in the operating room (OR), and the saline or lidocaine for injection was delivered to the OR in prefilled unlabeled syringes placed in an enve-

lope. The 5 mcg/kg dose of clonidine was chosen to allow patients to be within the common therapeutic daily dose of 0.2 to 0.6 mg.

Anesthesia

On arrival at the preanesthetic induction area, patients were administered midazolam (titrated to 5 mg IV in 0.5 mg increments) until they were drowsy but easily aroused by verbal command. Induction of anesthesia was initiated with fentanyl (2 to 5 mcg/kg IV) and followed by a sedative hypnotic (i.e., thiopental, etomidate, or propofol) selected at the discretion of the anesthesiologist based on the patients preoperative status. The hypnotic was titrated to achieve a computerized EEG pattern of delta, theta, and low alpha activity with a spectral edge frequency (SEF) of 10 to 14 Hz. This level of sedation was chosen because it was previously determined to be a depth of hypnosis that prevents major blood pressure responses to laryngoscopy.¹³ After complete muscle relaxation was obtained, as monitored by a peripheral nerve stimulator, 4% lidocaine (5 ml) was administered via direct laryngoscopy. Endotracheal intubation followed 1 minute later. Anesthesia was maintained with 50 to 70% nitrous oxide in oxygen, end-tidal isoflurane concentration of 0.1 to 0.4% and fentanyl 0.5 to 4 mcg/kg/hr IV, titrated to maintain a stable EEG pattern of delta, theta, and low alpha activity with a SEF of 10 to 14 Hz. Patients were kept paralyzed throughout the surgery, and the average end-tidal isoflurane concentration, rate of fentanyl infusion, and total dose of fentanyl were recorded.

Monitoring

In the operating room before anesthesia was induced but after each patient received midazolam (2 mg IV), EEG electrodes were placed after skin infiltration with 2% lidocaine, in a standard

frontal occipital montage for 2-channel computerized and raw EEG monitoring using the Neurotrac (Moberg Medical, Ambler, PA). In addition to routine monitoring, a radial artery catheter was placed for continuous blood pressure monitoring.

After induction of anesthesia and maintenance of a stable SEF at 10 to 14 Hz, MAP and heart rate (HR) were recorded 1 minute before intubation (baseline 1), during laryngoscopy, at 30 seconds, and 1 and 2 minutes after intubation. If HR or MAP increased more than 30% of baseline values, thiopental (50 mg IV) was given in repeated doses to return the hemodynamic parameters to this level.

The head holder was placed within 40 to 70 minutes of intubation under stable anesthetic conditions, which were titrated to the same EEG endpoint. MAP, HR, and SEF were recorded 1 minute before application of the head holder (baseline 2); at the time the skull-pin head holder was applied; and at 0.5, 1, 2, 3, and 4 minutes after placement. If MAP or HR increased by more than 30%, a rescue dose of thiopental (50 mg IV) was again administered and repeated as necessary to reduce MAP and HR to baseline 2 levels. If MAP and HR decreased more than 20% of the value of (baseline 2), ephedrine (5 mg IV) was given and repeated as necessary to restore these hemodynamic parameters to (baseline 2) levels.

Statistical Methods

Demographic data were recorded as were type of surgery and anesthetic requirements for each group. HR, MAP, and all other parametric values were compared between groups at each individual time point using repeated measures multiple analysis of variance. Intragroup changes were also compared to baseline values during both intubation and H-H placement. Categorical data were analyzed using Chi-square analysis. Significance was assessed at the 0.05 level.

RESULTS

Demographic data are presented in Table 1. Patients in all four groups were similar and received equivalent doses of fentanyl to induce anesthesia. Isoflurane concentrations during maintenance of anesthesia were also similar for all patients, except that one patient in Group 2 required a total intravenous technique that included propofol and fentanyl because of a suspected history of malignant hyperthermia. Hemodynamic data during laryngoscopy and intubation are presented in Figure 1.

Between group differences in MAP were minimal after intubation compared to the preoperative and baseline 1 time points. Preoperatively, HR tended to be lower in patients who received oral clonidine (Groups 1 and 2, Fig. 1). HR increased significantly during intubation and at the 1- and 2-minute time points after intubation in Groups 3 and 4 (Fig. 1). Both Groups 1 and 2 showed relatively little change in HR during intubation compared to Groups 3 and 4.

Hemodynamic data during pin head-holder placement are presented in Figure 2. HR varied minimally from the baseline 2 time point after H-H placement in Groups 1 and 3. HR in Group 4 increased rapidly 30 seconds after H-H placement and remained elevated over the next 3 minutes. In Group 2, HR slowly increased after H-H insertion and only became significantly elevated 3 minutes after the event (Fig. 2). MAP did not increase after head-holder placement in patients who received both clonidine and lidocaine (Fig. 2). In

patients who received clonidine alone with no scalp infiltration of lidocaine, no increase in MAP was noted. Lidocaine injected into the scalp before pin head-holder application, without the addition of clonidine (Group 3), produced no increase in MAP after H-H placement (Fig. 2). In the patients who were given a placebo for both clonidine and lidocaine (Group 4), MAP increased at the 30-second time point after H-H insertion and remained an average of 15 mm Hg higher than the other groups over the remaining 4 minutes of measurement (Fig. 2).

No significant clinical differences between the groups in the amount of anesthetic agents required for the surgical procedure were noted (Table 2). Two patients who received clonidine/lidocaine, two who received clonidine/placebo, and two who received lidocaine/placebo required thiopental rescue when MAP increased more than 30% of baseline during H-H placement, while three patients required rescue in the placebo/placebo group. One patient who received a placebo-placebo required rescue for MAP decrease of more than 20% of baseline values during H-H placement.

DISCUSSION

Clonidine appears to possess many properties that make it an appealing adjunct to the intraoperative management of neurosurgical patients. By stimulating α_2 -receptors, clonidine decreases total pe-

Table 1 Demographic Data: Clonidine Pin Head Holder Study

	Clonidine/ Lidocaine	Clonidine/ NS	Placebo/ Lidocaine	Placebo/ NS
Age	45.7 $\pm$ 6.3	50.9 $\pm$ 3.3	41.6 $\pm$ 3.6	46.4 $\pm$ 2.0
Height	171 $\pm$ 3.7	168 $\pm$ 3.3	168 $\pm$ 5.4	171 $\pm$ 2.3
Weight	75.6 $\pm$ 4.2	74.7 $\pm$ 4.4	72.7 $\pm$ 5.8	66.8 $\pm$ 4.8
M/F	5/2	2/5	2/7	4/7
Fentanyl dose (μ g) (induction)	279 $\pm$ 90	350 $\pm$ 65	342 $\pm$ 42	318 $\pm$ 44

Values represent MEAN $\pm$ SEM. No significant differences were noted.

Figure 1 Heart rate (HR) and mean arterial pressure (MAP) values measured preoperatively; 1 minute before intubation; at intubation; and 30 seconds, 1 minute, and 2 minutes after intubation. *p < 0.05 compared to clonidine/lidocaine. **p < 0.05 compared to clonidine/placebo.

Figure 2 Heart rate (HR) and mean arterial pressure (MAP) values 1 minute before H-H placement (baseline 2); at H-H placement; and 30 seconds, 1, 2, 3, and 4 minutes after H-H placement. +p < 0.05 compared to baseline 2. **p < 0.05 compared to H-H placement. +++p < 0.05 compared to 30 seconds after placement. ++++p < 0.05 compared to 1 minute after placement. *p < 0.05 compared to 2 minutes after placement. **p < 0.05 compared to 3 minutes after placement.

Table 2 Anesthetic Requirements of Groups

Group	Clonidine/ Lidocaine	Clonidine/ NS	Placebo/ Lidocaine	Placebo/ NS
Midazolam premed. (mg)	2.1 ± 0.5	2.3 ± 0.5	3.0 ± .05	2.6 ± 0.4
Fentanyl infusion (mcg/kg/hr)	2.5 ± 0.4	2.3 ± 0.4	2.4 ± 0.2	2.3 ± 0.1
Isoflurane (1% end-tidal)	0.5 ± 0.1	0.5 ± 0.1	0.6 ± 0.1	0.6 ± 0.1

Isoflurane data exclude the patient who received total intravenous anesthesia.
Values represent MEAN ± SEM. No significant differences were noted.

ripheral resistance, renal vascular resistance, HR, and blood pressure.^{2,14-15} This agent also slows cerebral electrical activity and decreases the cortical response to sensory input, which may partially explain the decrease in anesthetic requirements associated with clonidine administration.^{3-5,16} In neurosurgical patients clonidine lowers glucose, aldosterone, and plasma cortisol concentrations and does not affect intracranial pressure (ICP) as measured from cerebrospinal fluid pressure.^{11,17} Furthermore, clonidine decreases sympathetic overactivity in head-injured patients.¹⁸ This apparent inhibitory effect of clonidine on central monoaminergic systems has been suggested as an explanation for this agent's ability to blunt the hemodynamic response to noxious stimuli including endotracheal intubation.⁴

Control of hemodynamic parameters during neurosurgical procedures is of great concern to the neuroanesthesiologist whose goals include ensuring optimal cerebral perfusion pressure. In addition to endotracheal intubation and surgical incision, head-holder insertion is an intense nociceptive stimulus that dramatically increases MAP and HR.⁶⁻⁷ The head-holder device consists of a C-shaped metal clamp with three sharpened metal pins triangularly arranged to fit on the skull. In most institutions, the pins are tightened until they press into the skull of the anesthetized patient with 80 pounds of pressure. Unlike stimulation by endotracheal intubation, which varies with the skill of the anesthesiologist, type of endotracheal tube, and anatomy of the larynx, the placement of the head holder is a more reproducible stimulus each time it is applied. This "uniform" stimulus should be

blunted in neurosurgical patients to avoid unwanted increases in blood pressure, HR, and ICP.

In our study, baseline HR was lower in patients who received clonidine. The addition of clonidine to the anesthetic attenuated the HR response to laryngoscopy not observed in patients who received the placebo. This finding agrees with other studies that have demonstrated a bradycardic or no response in HR to intubation after clonidine pretreatment.¹⁹⁻²⁰ The addition of clonidine also reduced baseline MAP compared to those who received a placebo. However, no difference was noted between groups in blood pressure response to laryngoscopy. This finding may reflect the level of anesthesia to which the patients were titrated. Each patient's anesthetic depth was standardized by EEG and maintained at a SEF of 12 to 14 Hz. None of the other studies that evaluated the effects of clonidine premedication used this method to standardize the level of anesthesia during noxious stimulation. It is probable that minimal blood pressure changes were recorded during intubation in all patients because depth of anesthesia was sufficient to negate any response.

Clonidine alone attenuated the rise in MAP but not in HR observed after pin H-H placement in the placebo group. No increases in HR or MAP were noted after H-H application in all patients who received scalp infiltration of lidocaine. In contrast, in the placebo group, both HR and MAP increased after H-H placement. These results agree with those of Chadha et al.¹⁹ who found a diminished hypertensive response after laryngoscopy and H-H placement in patients who received oral clonidine. Favre et al.¹¹ compared a placebo to

clonidine for H-H placement and found that MAP increased significantly from baseline in both groups. However, they did demonstrate a significantly lower baseline MAP 4 minutes after clonidine administration as well as at all time points during H-H placement compared to the controls. This difference between groups was not present in our study, perhaps reflecting the use of oral rather than intravenous clonidine. Intravenous clonidine peaks rapidly in plasma (2 to 28 minutes) compared to oral clonidine, which peaks within 90 minutes.^{14,21} Thus, the intravenous form of clonidine has a more rapid and profound effect than the oral form and may have produced the differences between the studies. Lidocaine injected at the site of pin H-H placement attenuated the rise in HR and MAP observed in the placebo group. Our findings with lidocaine support those of other studies demonstrating its effectiveness in blunting the hemodynamic response to head-holder placement.^{7,11,14} In the combination group (clonidine/lidocaine), MAP and HR responses were the same as in the patients who received a lidocaine scalp injection alone. Combination oral clonidine and lidocaine scalp injection at the pin H-H sites blunted the blood pressure and HR responses observed in the placebo group. Lidocaine injection alone demonstrated a similar response. Oral clonidine reduced the blood pressure response to H-H placement but could not attenuate the HR response. Thus, oral clonidine was not as effective as lidocaine injection in reducing hemodynamic responses to H-H placement. No additional benefit was noted when clonidine and scalp injection of lidocaine were given in combination. This finding agrees with another study that used a lower dose of clonidine (3 mcg/kg).¹² Thus, even at the higher concentrations of clonidine used in the present study, no beneficial effect on HR response during H-H application was noted.

Hypotension is a potentially dangerous effect of clonidine in combination with anesthetic induction agents. One minute before H-H placement, one patient in the placebo group required

rescue treatment for hypotension with none of the patients who received clonidine needing treatment for low blood pressure. In a previous study rescue treatment was required for eight patients in the clonidine group compared to two patients in the placebo group where cerebral perfusion pressure was less than 60.¹¹ This difference also may be associated with the method of clonidine administration. Intravenous clonidine may be more potent and produce a more hypotensive effect compared to the orally administered form.

Clonidine also decreases anesthetic drug requirements.³⁻⁵ We found no differences in the anesthetic requirements in our four study groups. During craniotomies, a conscious effort is made to have patients be awake and able to cooperate with a neurological examination after the neurosurgical procedure is complete. With anesthetic agents strictly titrated to ensure this outcome, significant reductions in anesthetic requirements may not be as notable in our study population as in patients undergoing coronary artery bypass procedures.³ Furthermore, our patient population was free of associated medical conditions like peripheral vascular disease and renal insufficiency, which may affect the clearance of clonidine.²²

This study could be criticized on the basis of population size and the possible lack of power. During the study, patient-admitting practices changed at both institutions. This population of skull base patients who first were admitted the day before surgery were later admitted the day of surgery. This change was thought to alter the study population baseline variables by altering the amount of stress that patients might experience before surgery. This change in preoperative stress levels could change hemodynamic variables and produce a difference compared to patients who were admitted the night before surgery. This potential for an uncontrolled difference attributable to admitting practices forced the premature closure of the study. However, despite the small size of the population, groups were significantly different, adding validity to the results.

CONCLUSION

In conclusion, oral clonidine appears to have a positive effect on the prevention of abrupt increases in HR observed during laryngoscopy and MAP associated with H-H placement. The addition of lidocaine to the scalp was most effective in reducing the hemodynamic response to H-H placement. This study demonstrates that clonidine given orally does not produce significant hypotension and is beneficial when used in combination with scalp injection of lidocaine to reduce the detrimental hemodynamic changes associated with both laryngoscopy and H-H placement. However, oral clonidine alone is not as effective as lidocaine scalp injection in blunting the hemodynamic response to H-H placement.

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