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Original Article

Anaesthesia Section

# Preoperative Clonidine with Perioperative Dexmedetomidine for Attenuating Haemodynamic Responses and Blood Loss in Patients Undergoing Elective Transnasal Transsphenoidal Resection of Pituitary Tumours: A Randomised Clinical Study

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## ABSTRACT

**Introduction:** Transsphenoidal resection of pituitary tumours presents challenges for an anaesthesiologist due to haemodynamic fluctuations caused by intense nociceptive stimuli during different surgical stages. This relatively short procedure requires a smooth and rapid emergence for spontaneous airway control and assessment of surgical outcomes. Therefore, the chosen anaesthetic agent should provide effective haemodynamic control and facilitate rapid recovery. Alpha-2 agonists such as dexmedetomidine and clonidine are known to centrally decrease noradrenaline release, thus reducing sympathetic outflow. This could be particularly beneficial in minimising haemodynamic fluctuations during such surgeries.

**Aim:** To compare the effects of preoperative clonidine and perioperative dexmedetomidine in attenuating haemodynamic responses and blood loss in patients undergoing elective Transnasal Transsphenoidal (TNTS) resection of pituitary tumours.

**Materials and Methods:** A randomised, double-blinded study was conducted in the Department of Neuroanesthesiology at Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India, over a period of one year, from February 2022 to January 2023. Sixty patients of either sex, aged 18-65 years with ASA I or II, scheduled for elective TNTS pituitary surgery, were enrolled and divided into group A and group B. Group A received clonidine tablets (3 mcg/kg) 180 minutes prior to surgery, while group B received intravenous (i.v.) infusion of dexmedetomidine (1 mcg/kg/min) over 10 minutes before induction, followed by 0.5-0.7 mcg/kg/hr. Group A received a placebo of 0.9% Normal Saline (NS) (50 mL). Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Mean Arterial Pressure (MAP) were recorded at baseline, intubation, nasal pack insertion, endoscope insertion, and at various time intervals. Data obtained were analysed using unpaired sample t-test for independent groups, and Chi-square test was used for categorical data. A probability value of 0.05 was considered significant for both statistical tests.

**Results:** The mean age of participants was 42±11 years for group A and 43±12 years for group B, with a male: female ratio of 66.6% to 33.3% in group A and 70% to 30% in group B, respectively. The mean Body Mass Index (BMI) was 26.4±3.2 in group A and 25.2±1.7 in group B. HR, SBP, and MAP decreased at various stages in group B compared to group A, and these differences were statistically significant (p-value <0.05). The study also found that the total consumption of propofol was significantly less in group B (220±38) compared to group A (282±140). Similarly, total fentanyl consumption was significantly lower in group B (5.83±1.60) than in group A (16.6±23.9). Although not statistically significant, total blood loss was also lower in group B (115±63) compared to group A (156±108).

**Conclusion:** Intraoperative infusion of i.v. dexmedetomidine provides a reasonable choice compared to orally administered clonidine for transsphenoidal pituitary tumour resection, considering its favorable effects on haemodynamic stability and anaesthetic requirements.


**Keywords:** Airway control, Alpha-2 agonists, Surgical outcomes

## INTRODUCTION

The TNTS approach for pituitary tumour resection provides the advantage of early midline access to the sella, along with minimal trauma, a low risk of haemorrhage, and decreased complications [1]. However, it poses many challenges such as hypertension due to nasal packing with lignocaine with adrenaline and surgical stress [2]. At the end, it is important to ensure early recovery since the surgical duration is a short, patients have a nasal pack which obligates them to breathe through their mouth, making awake extubation essential [3]. The main purpose of anaesthesia is to maintain haemodynamic stability, provide a good surgical field, and ensure a smooth emergence. Numerous studies have been conducted to observe the effects of various anaesthetic agents, as well as, regional anaesthesia techniques like bilateral maxillary nerve block and bilateral sphenopalatine ganglion block [2,4]. Surgical stimulus generates a stress response through sympathetic stimulation, leading to an increase in pituitary hormones [5].

Dexmedetomidine and clonidine are known to decrease central noradrenaline release, thereby reducing sympathetic outflow. Both dexmedetomidine and clonidine are alpha-2 agonists.

Dexmedetomidine is a selective alpha-2 agonist (with an $\alpha2:\alpha1$ selectivity ratio of 1620:1) that possesses analgesic and sedative properties while also having an anaesthetic and opioid-sparing effect [6]. Dexmedetomidine binds to the $\alpha2$ receptor eight times more strongly than clonidine and has a comparatively shorter duration of action [7]. Various studies have also compared the effects of intravenous dexmedetomidine and clonidine on haemodynamics in pituitary, cranial, and nasal surgeries [8,9]. However, there are a limited number of studies comparing the effects of orally administered clonidine with intravenous dexmedetomidine [1]. The present study primarily aimed to compare preoperative clonidine with perioperative dexmedetomidine in attenuating the haemodynamic responses in patients undergoing elective TNTS resection of pituitary tumours. The secondary aim was to compare the total dose of propofol and fentanyl administered, as well as, the total blood loss during the surgery.

## MATERIALS AND METHODS

This randomised clinical study was conducted in the Department of Neuroanaesthesiology at Mahatma Gandhi Medical College and Hospital in Jaipur, India. The duration of the study was one year, from February 2022 to January 2023. The study received approval from the Institutional Ethical Committee (reference number MGMCH/IEC/JPR/2020/39) and was registered with CTRI (CTRI/2021/03/032035). Our clinical research was conducted in accordance with the Ethical Principles for Medical Research Involving Human Subjects outlined in the Helsinki Declaration of 1975 (revised in 2000).

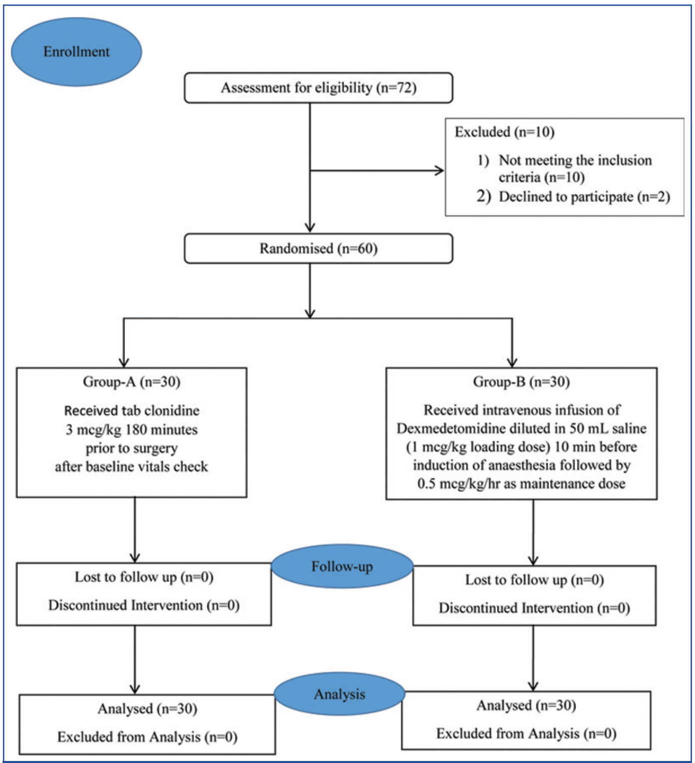
**Inclusion criteria:** Patients of either sex, aged between 18 and 65 years, belonging to American Society of Anesthesiologists (ASA) Grade-I and II, who were scheduled for elective TNTS pituitary surgery were included in the study.

**Exclusion criteria:** Patients with a Glasgow Coma Scale (GCS) less than 15, preoperative HR less than 50 beats/min, pregnant patients, those taking antihypertensive drugs, patients with pre-existing psychiatric or neurological illnesses, emergency pituitary surgery in case of bleeding, allergy to dexmedetomidine and opioids, morbid obesity, and those who refused to give consent were excluded from the study.

**Sample size calculation:** The sample size was calculated using the formula:

$$n \geq Z^2{}_{1-\alpha/2} \times p(1-p)/d^2$$

with reference values of Alpha-0.05, estimated population (p)-0.08, and estimated error (d)-0.07. Based on the calculation, a sample size of 60 was required [Table/Fig-1].



**[Table/Fig-1]:** CONSORT diagram.

### Study Procedure

Written informed consent was obtained from each participant. During the preoperative visit, patients underwent a thorough examination, their medical history was recorded, and age, sex, and BMI were noted. Patients were instructed to fast for six hours for solids and two hours for clear liquids. They were also given a tablet of pantoprazole 40 mg on the night before surgery with sips of water. On the scheduled day of surgery, patients were randomly assigned to groups using the chit method, where they picked a chit indicating their group allocation. Based on that, they were divided into two groups, A and B. Patients were unaware of their assigned group. All drugs were prepared by a resident who was not involved in the study. The person administering the drugs was unaware of the syringe contents, and the investigator was also unaware of the drugs given, ensuring a double-blinded study. Group A patients were administered tab clonidine 3 mcg/kg (tab Arkamine by Torrent Pharmaceuticals Ltd., India), while Group B patients received tab zinc sulfate 10 mg (tab opizin-10 mg by GP Pharma International, Nagpur, Maharashtra, India) as a placebo 180 minutes prior to surgery, after baseline vital signs check. Previous studies by Jan S et al., and Mariappan R et al., used tablet clonidine 200 mcg, which is approximately 3 mcg/kg, so it was decided to use a 3 mcg/kg dose in the present study [1,9]. Group B patients received an intravenous (i.v.) infusion of dexmedetomidine (inj dextomid 200 mcg by Neon Laboratories Ltd., India) diluted in 50 mL saline (1 mcg/kg loading dose) over 10 minutes before anaesthesia induction, followed by 0.5 mcg/kg/hr as a maintenance dose. Patients in Group A received 0.9% NS 50 mL as a placebo, administered as an infusion similar to Group B. A total of 50 mL of dexmedetomidine infusion was prepared by using 200 mcg (2 mL) of dexmedetomidine and adding 48 mL of saline, resulting in a concentration of 4 mcg/mL. Dexmedetomidine was administered as a loading dose of 1 mcg/kg/min over the first 10 minutes, followed by 0.5 mcg/kg/hr as a maintenance dose [2].

An i.v. 18 G or 20 G cannula was secured, and standard monitoring as per ASA guidelines, including electrocardiogram, pulse oximetry, non-invasive blood pressure, and skin temperature probe, were attached. After anaesthesia induction, a radial artery was cannulated with a 20 G arterial cannula for Intrarterial Blood Pressure (IABP) monitoring. Standard general anaesthesia induction was performed using inj. fentanyl 2-3 mcg/kg i.v., inj. glycopyrrolate 0.2 mg i.v., inj. propofol 2-3 mg/kg i.v., and inj. vecuronium 1 mg/kg i.v. In cases of anticipated difficult intubation, inj. rocuronium 0.9 mg/kg i.v. was administered, while ensuring availability of sugammadex. Throat packing was done using moist cotton gauge under direct laryngoscopy to avoid trickling of betadine and blood into the oesophagus and trachea. Anaesthesia was maintained with i.v. propofol infusion and a mixture of oxygen, air, and isoflurane (MAC of 0.5) under Bispectral Index (BIS) guidance (Covidien BIS™ LOC 4-Channel Monitor with Patient Interface Cable). The target BIS value was maintained at 40-60. In Group A and B, respective infusions (NS and Dexmedetomidine) were started. Haemodynamic parameters, including HR, SBP, DBP AND MAP were noted at baseline, at the time of intubation, at nasal pack insertion, at the time of insertion of endoscopy, at 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120 minutes, five minutes prior to extubation, and at the time of extubation. Intraoperatively, if an increase in HR and MAP ≥20% of the baseline was noted, an i.v. bolus of inj. fentanyl 1 mcg/kg was administered, provided the time since the last dose of fentanyl given was more than 30 minutes. If there was still an increase in MAP, an additional bolus of propofol was given. Throughout the surgery, a forced-air warming device was used to maintain normothermia. Towards the end of the surgery, inj. paracetamol 15 mg/kg i.v. infusion and inj. ondansetron 4 mg i.v. were given. At the conclusion of the surgery, all infusions and isoflurane were stopped, and the patient was taken on 100% oxygen to prepare for extubation. To reverse the residual effects of neuromuscular blocking agents, inj. neostigmine 0.05 mg/kg i.v. and inj. glycopyrrolate 0.01 mg/kg i.v. were given. Extubation was performed once the patient was able to protect their airway, generate adequate tidal volume, and follow all commands. Total propofol, fentanyl consumed, and blood loss during the surgery were also noted. Patients were then shifted to the neuro Intensive Care Unit (ICU) for further observation and care.

## STATISTICAL ANALYSIS

The collected data were analysed using IBM Statistical Package for Social Sciences (SPSS) software version 23.0. Descriptive statistics, including frequency analysis and percentage analysis, were used for categorical variables, while the mean and standard deviation were used for continuous variables. The unpaired sample t-test was used to determine significant differences between bivariate samples in independent groups. The Chi square test was used to determine the significance in categorical data. A p-value of 0.05 was considered significant.

## RESULTS

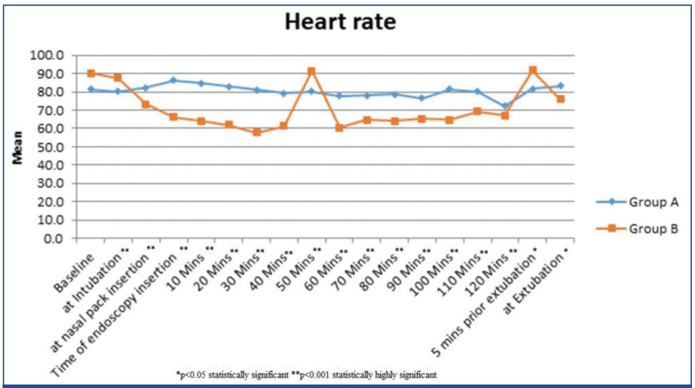
The mean age of patients in Group A and B was noted to be 42 and 43, respectively as shown in [Table/Fig-2], which was comparable and statistically not significant. The total number of males and females was 68.3% and 31.7%, respectively. In Group A, 66.6% were males and 33.3% were females, while in Group B, 70% were males and 30% were females. The mean BMI was noted to be 26.4±3.2 in Group A and 25.2±1.7 in Group B. The p-value was found to be 0.068, which is not significant.

| Variables | Group A | Group B | p-value |
|---|---|---|---|
| Age (in years) | 42±11 | 43±12 | 0.663 |
| ASA grade | 24:6 | 25:5 | 0.334 |
| BMI (in kg/m²) | 26.4±3.2 | 25.2±1.7 | 0.068 |
| Sex (male: female) | 20:10 (66.6%:33.3%) | 21:9 (70%:30%) | 0.677 |
| Duration of surgery (in minutes) | 110.6±17.9 | 111.4±18.5 | 0.888 |

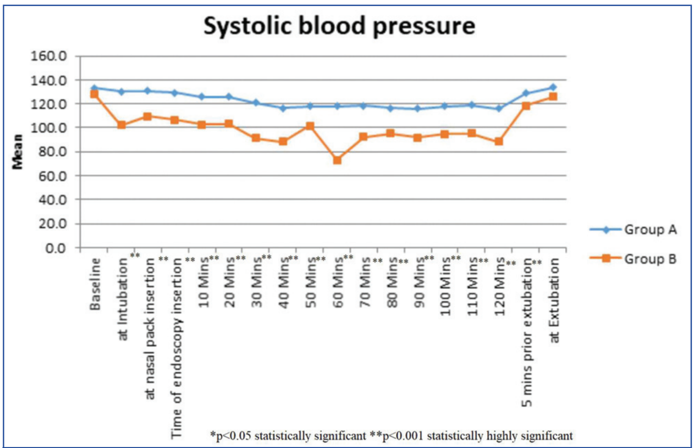
**[Table/Fig-2]:** Demographic profile of the patients in both the groups.
p>0.05 not significant, *p<0.05 statistically significant, **p<0.001 statistically highly significant; ASA: American society of anesthesiologists; BMI: Body mass index

In both groups, a decrease in HR, SBP, DBP, and MAP was seen at various time intervals, which was found to be statistically significant or highly significant as shown in [Table/Fig-3-6]. This implies that both study drugs blunt the responses at various times during the surgery. However, when comparing the two drugs, it is found that dexmedetomidine more efficiently blunts the sympathetic responses in terms of HR, SBP, DBP, and MAP compared to clonidine.

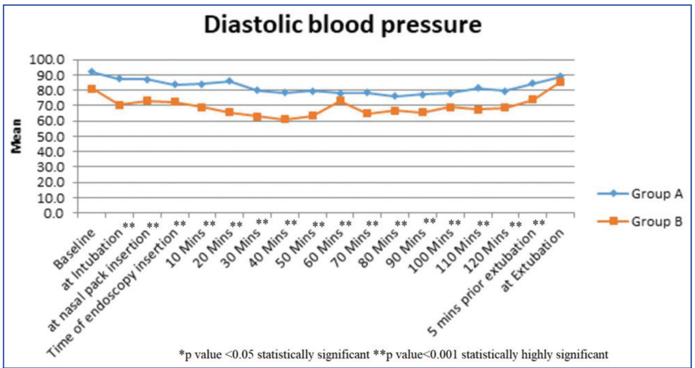
In terms of total propofol consumed, [Table/Fig-7] shows that in Group A, the total propofol consumed was 282±140, while in Group B, it was 220±38. Therefore, both agents reduce the need for propofol, but this reduction was found to be significant in the dexmedetomidine group. It was observed that the total



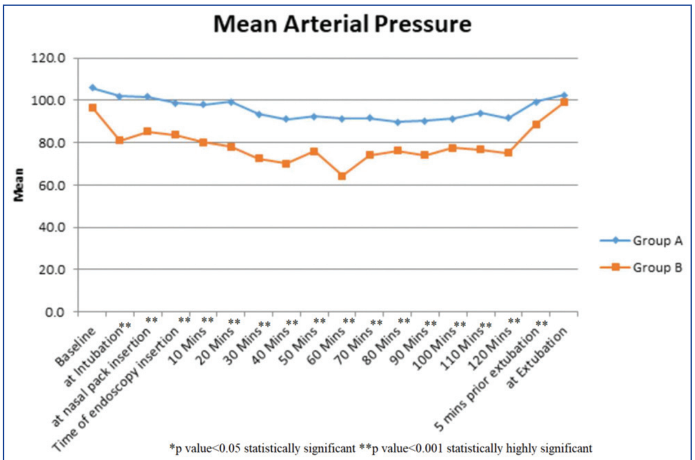

**[Table/Fig-3]:** Comparison of Heart Rate (HR) at various time intervals in both the groups.




**[Table/Fig-4]:** Comparison of Systolic Blood Pressure (SBP) at various time intervals in both the groups.




**[Table/Fig-5]:** Comparison of Diastolic Blood Pressure (DBP) at various time intervals in both the groups.




**[Table/Fig-6]:** Comparison of Mean Arterial Pressure (MAP) at various time intervals in both the groups.

fentanyl consumption was 16.6±23.9 in Group A and 5.83±1.60 in Group B, indicating that dexmedetomidine significantly decreases the need for fentanyl. However, the total blood loss during the surgery was not significantly different between the two groups. It was observed that blood loss was less in Group B, although not statistically significant.

| Variables | Group A | Group B | p-value |
|---|---|---|---|
| Total propofol consumed | 282±140 | 220±38 | 0.025* |
| Total fentanyl consumption | 16.6±23.9 | 5.83±12.60 | 0.032* |
| Blood loss | 156±108 | 115±63 | 0.077 |

**[Table/Fig-7]:** Total propofol, total fentanyl consumption and blood loss intraoperatively in both the groups.
p>0.05 not significant, *p<0.05 statistically significant, **p<0.001 statistically highly significant

## DISCUSSION

During the Transnasal Transsphenoidal (TNTS) resection of pituitary tumours, there is a wide fluctuation in haemodynamic parameters, especially hypertension and tachycardia, at various steps of the surgery. This is due to the strong noxious stimulus, absorption of vasopressor drugs like adrenaline soaked in nasal packs, and rich sensory innervation in the nasal mucosa. Providing a clear surgical field is a prerequisite for endoscopic surgeries, and increased HR and blood pressure can lead to increased bleeding, which can obscure the surgical field view [10]. Additionally, relative bradycardia can aid in reducing capillary oozing in the surgical field [11]. Deep general anaesthesia using inhalational agents and opioids may not effectively suppress the haemodynamic response to the noxious stimulus, and can result in compromised arterial blood pressure and decreased blood flow to vital organs, predisposing the patient to ischaemia, especially cerebral hypoperfusion, which can be detrimental [12]. Conversely, sudden increases in blood pressure can cause oedema and more bleeding in the surgical field. Therefore, it is of utmost importance for an anaesthesiologist to control all haemodynamic parameters and maintain optimal perfusion of vital organs during these surgeries.

During emergence from anaesthesia, an anaesthesiologist must strike a balance between two opposing goals. Deep extubation poses a risk of airway obstruction, especially in patients with nasal packs and hormonal imbalances or anatomical changes that make them susceptible to airway obstruction. On the other hand, if the patient coughs on the endotracheal tube, there is a risk of dislodging sealing agents and causing bleeding from the surgical site. Another challenge for the anaesthesiologist is to ensure early recovery to facilitate postoperative neurological assessment [2]. Selective alpha 2 agonist agents, such as clonidine and dexmedetomidine, have been extensively studied as hypotensive agents in these situations. They have a lower risk of respiratory depression, which is an additional advantage [6,7].

The authors decided to administer oral clonidine as it is convenient and provides the additional benefit of reducing anxiety. Administration via the oral route is preferred over other routes, as it avoids needle pricks and improves patient compliance. The bioavailability of clonidine after oral administration is 75%-100%, and it carries a lower risk of sedation and respiratory depression [13]. The present study demonstrated a decrease in HR, SBP, and DBP at various intervals throughout the surgery, and this decrease was significantly greater in Group B (p<0.05), indicating that dexmedetomidine offers a better haemodynamic profile compared to clonidine. These findings are consistent with other studies conducted by Jan S et al., Sairam PV et al., and Bafna U et al., where they showed that dexmedetomidine provides a better haemodynamic profile, improved operative field, conscious sedation, and analgesia, respectively [1,5,12].

The study also evaluated the total consumption of propofol, which was observed to be 282±140 in Group A and 220±38 in Group B. There was a significant reduction in propofol consumption in Group B compared to Group A, indicating that dexmedetomidine reduces the need for additional agents. Similarly, the study evaluated the total fentanyl consumption, which was significantly lower in Group B (5.83±12.60) compared to Group A (16.6±23.9). These findings are consistent with a study conducted by Gopalakrishna KN et al., where they showed lower fentanyl consumption in the dexmedetomidine group [3].

### Limitation(s)

Several limitations were present in the present study. Firstly, the tumour size was not taken into account, and larger tumour sizes are associated with a higher risk of bleeding. Secondly, the surgeon satisfaction score regarding the quality of the surgical field was not documented. Additionally, only ASA Grade-I and II patients were included, and the study did not consider patients with poor cardiac reserve who may experience deleterious effects from bradycardia and hypotension caused by dexmedetomidine and clonidine. Future research could focus on measuring stress hormone levels like cortisol preoperatively and postoperatively, as this could provide valuable insights into stress response attenuation.

## CONCLUSION(S)

During intraoperative TNTS pituitary tumour resection, both intravenous dexmedetomidine and orally administered clonidine are viable options for attenuating the stress response. However, when choosing between these two agents, intravenous dexmedetomidine infusion is a better choice as it provides better haemodynamic conditions and reduces the need for additional agents like propofol and fentanyl.

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