

Preoperative anxiety correlates with propofol-induced hypotension during induction of general anesthesia in females undergoing elective gynecological surgery : an observational study

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Abstract : Purpose. Pre-operative anxiety causes marked reduction in blood pressure after spinal anesthesia in women undergoing caesarean delivery. As inhibition of the sympathetic system is one of the mechanisms of hypotension from propofol, patients having a heightened sympathetic tone might have an exaggerated hypotension due to propofol. We designed this study to know the correlation between preoperative anxiety and propofol-induced hypotension

Methods : One hundred female patients of American Society of Anesthesiologist physical status I or II has been recruited in this prospective observational study. Anxiety was assessed one day before surgery by two validated scales of anxiety, namely verbal analogue scale (VAS-A) of anxiety score, and generalised anxiety disorder-7(GAD-7) questionnaire. Primary outcome was correlation between GAD-7 score and VAS-A with absolute maximum change in MAP during the first 10 minutes (Δ MAP), maximum change in SBP during the first 10 minutes (Δ SBP), and maximum change in DBP during the first 10 minutes (Δ DBP) after the administration of propofol.

Results : A significant correlation was found between GAD-7 score and Δ SBP ($p < 0.0001$), Δ DBP ($p = 0.022$) and Δ MAP ($p = 0.002$). However, a significant relation was found only between VAS-A and Δ SBP ($p < 0.0001$). A significant correlation was found between GAD-7 score and $\% \Delta$ SBP ($p < 0.0001$) and $\% \Delta$ DBP ($p = 0.004$). Similarly, a significant correlation was found between VAS-A and $\% \Delta$ SBP ($p < 0.0001$).

Conclusion : Preoperative anxiety measured by simple scales such as VAS-A or GAD-7 correlates with propofol-induced hypotension in adult female patients during induction of general anesthesia.

Key words : propofol; anxiety; hypotension; general anesthesia

INTRODUCTION

Propofol is the most common intravenous agent used for the induction of general anesthesia in most areas of the world. Rapid onset and offset of action even after prolonged infusion, favorable operative conditions, and precise control over

sedation are some of the many advantages of using propofol (1,2). Along with this, propofol has antiemetic, antipruritic, and anticonvulsant action, which may be useful in several clinical situations (2). However, propofol has a number of potential adverse effects, including hemodynamic instability, pain on injection, dystonic movements, hypertriglyceridemia, pancreatitis, allergic reactions, or propofol infusion syndrome (3,4). In one study, the overall incidence of propofol-induced hypotension was 15.7%, and a 77% incidence was recorded within 10 min of induction of anesthesia (5). Females and elderly patients are particularly susceptible to hypotension from propofol. Hypotension is more problematic in hypertensive patients, patients having ischemic heart disease, and those with cerebrovascular disease (3).

The mechanism of propofol-induced hypotension is multifactorial, and thought to be mediated by the inhibition of the sympathetic nervous system, impairment of the baroreceptor reflex regulatory mechanisms (6), and direct relaxant effect on venous smooth muscles (7). Propofol has also a negative inotropic effect on the heart, and moderate depressive effect on the cardiac function (8). Patients suffering from a generalized anxiety disorder are in a state of a higher baseline sympathetic activity, which has been measured by continuous minute-to-minute skin conductance, motor activity, and 24 h ambient temperature in several published papers (9). A previous study has reported that pre-operative anxiety causes marked

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reduction in blood pressure after spinal anesthesia in women undergoing cesarean delivery (10). As inhibition of the sympathetic system is one of the proposed mechanisms of hypotension due to propofol, patients having a heightened sympathetic tone might have an exaggerated hypotension due to propofol administration. Hence, we hypothesized that patients with anxiety will experience exaggerated hypotension following induction with propofol during general anesthesia. This prospective observational study has been designed to find out the correlation between preoperative anxiety and propofol-induced hypotension. Data of the 29 included patients were presented at the 75th National Scientific Congress of the Australian Society of Anesthesiologists.

METHODS

After approval by our Institutional Ethics Committee, this study was conducted on 100 adult female patients of American Society of Anesthesiologists physical status I and II, undergoing gynecological surgeries. This study has been registered in the National Clinical Trial Registry of India (www.ctri.nic.in; CTRI/2017/10/010065).

Patients with ASA grade 3 or above, age >60 years, preoperative hypotension (SBP <90 mmHg), hypertension (SBP >140 mmHg), history of diabetes, peripheral vascular disease, ischemic heart disease, any psychiatric diseases and patients with a history of allergy to egg proteins were excluded from the study. A written consent form was obtained from all patients.

Anxiety was measured one day before surgery. Anxiety was assessed by two validated scales of anxiety, namely the verbal analog scale (VAS-A) of anxiety score, and generalized anxiety disorder-7 (GAD-7) questionnaire. Preoperative anxiety was assessed by either of the two study authors (AS or NN). In the VAS anxiety score, participants were asked to rate their anxiety on a scale of 0 to 10, where 0 represents no anxiety at all, and 10 represents the maximum possible anxiety level. Patients were categorized into mild (score of 0-3), moderate (score of 4-6), and severe (score of 7-10) anxiety group respectively. GAD-7 questionnaire has 7 questions and each question has 4 responses. Patients were asked to mark the appropriate response according to the bothering symptoms during the last 2 weeks. This was calculated by assigning scores of 0, 1, 2, and 3, to the response categories. These categories were not at all, several days, more than half the days, and nearly every day, respectively. Total

score ranges from 0 to 21. Severity was assessed by cut off scores of 5, 10, and 15, representing mild, moderate, and severe anxiety, respectively.

Standard ASA fasting guidelines were followed in all patients, and none of them received any premedication. In the operation theatre, patients were made supine and 5 lead ECG monitor, noninvasive blood pressure cuff, and pulse oxymetry probe were attached. Base line systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MAP), heart rate (HR), and SpO₂ were recorded for all patients. Thereafter, a 20 G intravenous catheter was secured over the dorsum of the hand. All patients were preoxygenated for 3 minutes with 100% oxygen, and general anesthesia was induced using 2 mg/Kg propofol, mixed with 2 ml of 2% xylocaine and administered over 30 sec through an infusion pump. SBP, DBP, MBP, and HR were recorded every 1 min up to 10 min after induction. Additional 20 mg propofol boluses were given every 1 min when there was no loss of verbal contact after the initial dose of propofol. The number of additional propofol boluses after the standard induction dose was also documented. A SBP less than 100 mmHg was treated with a 250 to 500 mL of fluid (normal saline/ ringer lactate) bolus. If SBP was not raised with fluid, ephedrine 5 mg boluses were repeated every 2 minutes to maintain a SBP >100 mmHg. All patients were mask ventilated with 50% oxygen, nitrous oxide, and 1% isoflurane after loss of verbal contact. Anesthetic gas flow was kept at 5 to 10 L/min, with a PEEP of 5 cm of H₂O to maintain an airway pressure between 15 and 20 cmH₂O. Patients were ventilated with a tidal volume of 6 to 8 mL/Kg body weight, and respiratory rate was adjusted to maintain the end-tidal CO₂ partial pressure between 35 and 40 mmHg. Any side effects like pain on injection, laryngospasm, difficulty to ventilate, desaturation, abnormal movement, or allergic reaction were noted. After 10 min, fentanyl 2 µg/Kg body weight and atracurium 0.5 mg/Kg body weight was given, and the patient's trachea was intubated.

Statistical analysis

Demographic (age, height, and weight), and baseline hemodynamic data (HR, SBP, MAP, DBP and SpO₂) were expressed as mean ± SD. GAD-7 score and VAS-A score were expressed as median and inter-quartile range. Correlation between GAD-7 score and VAS-A with absolute maximum change in MAP during the first 10 min (Δ MAP), maximum change in SBP during the first 10 min (Δ SBP),

and maximum change in DBP during the first 10 minutes (Δ DBP) were calculated by the Kendell's tau method. We avoided Pearson's correlation because it is easily affected by the outliers, and there is some evidence that Kendell's tau is better than Spearman's correlation (11). Maximum change in blood pressure values were analyzed as continuous data. Statistical significance was assumed if $p < 0.05$. As there was a directional hypothesis (i.e. higher anxiety level was associated with higher fall of blood pressure due to propofol), one-tailed tests were used. All statistical analyses have been performed using the SPSS statistical software (IBM SPSS Statistics for Mac, Version 21.0. IBM Corp, Armonk, NY).

RESULTS

Data of one hundred female patients were included in this study. Baseline demographic characteristics of the patients are provided in Table 1. The induction dose of propofol, additional requirements of propofol, total dose of propofol, baseline and pre-induction hemodynamic data are provided in Table 2. A significant correlation was found between GAD-7 score and Δ SBP ($\tau_\beta = 0.281, p < 0.0001$), Δ DBP ($\tau_\beta = 0.144, p = 0.022$) and Δ MAP ($\tau_\beta = 0.203, p = 0.002$) (Fig. 1). However, a significant correlation was found only between VAS-A and Δ SBP ($\tau_\beta = 0.284, p < 0.0001$). A significant correlation was found between GAD-7 score and $\% \Delta$ SBP ($\tau_\beta = 0.273, p < 0.0001$) and $\% \Delta$ MAP ($\tau_\beta = 0.185, p = 0.004$) (Fig. 2). Similarly, a significant correlation was found between VAS-A and $\% \Delta$ SBP ($\tau_\beta = 0.270, p < 0.0001$). Correlation between the changes in blood pressure and anxiety scores is provided in Table 3. A multivariate logistic regression model found that both anxiety levels measured by GAD-7 score and total dose of propofol affected the percentage of change in MAP ($p = 0.005$ and $p = 0.044$, respectively). However, the percentage of change in systolic blood pressure was

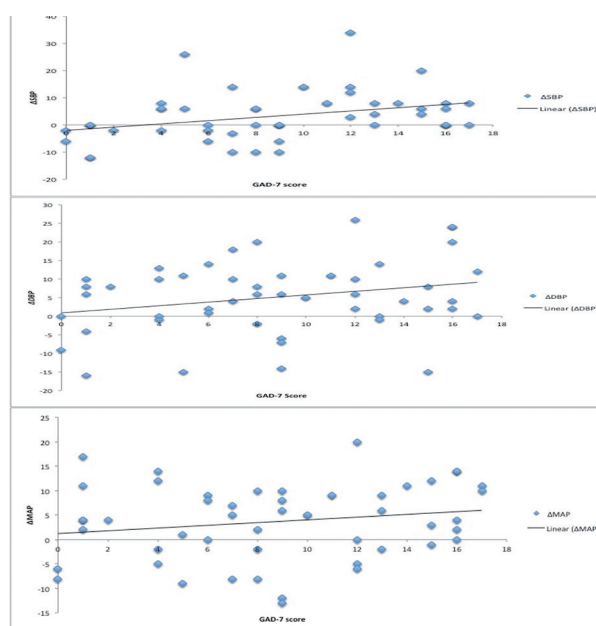


Fig. 1. — Scatter dot diagram showing the correlation between GAD score, Δ SBP, Δ DBP and Δ MAP.

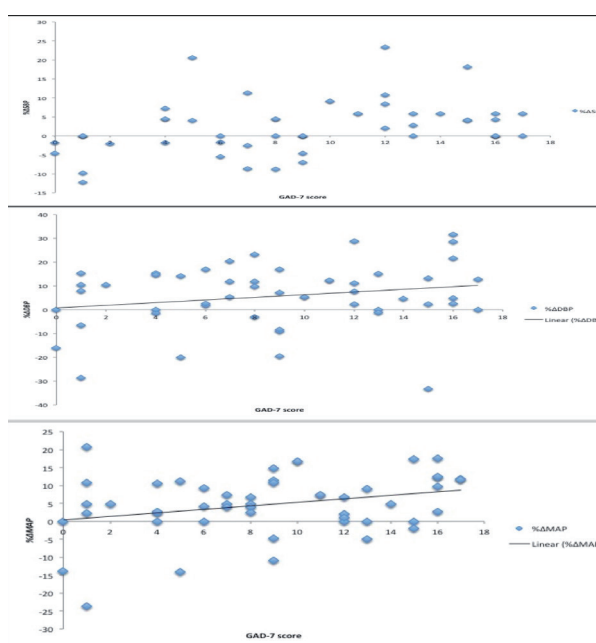


Fig. 2. — Scatter dot diagram showing the correlation between GAD score, $\% \Delta$ SBP, $\% \Delta$ DBP and $\% \Delta$ MAP.

Table 1

Baseline demographic parameters of the patients (Data expressed as mean \pm SD or proportions, as applicable) (n = 100).

| Parameters | |
|------------------|------------------|
| Age (Yr) | 31.06 \pm 4.7 |
| Body weight (Kg) | 62.03 \pm 10.1 |
| Height (cm) | 153.98 \pm 5.6 |
| ASA PS (I/II) | 76/24 |

ASA PS: American Society of Anesthesiologists' physical status.

neither associated with preoperative anxiety or total induction dose of propofol. Percentage of change in DBP was only associated with preoperative anxiety level ($p = 0.001$), but not with the total induction dose of propofol ($p = 0.107$). There was a significant correlation between VAS- A and GAD-7 ($p < 0.0001$).

Table 2
Propofol requirement and baseline hemodynamic data (Data expressed as mean \pm SD or median (range), n = 100).

| Parameters | |
|---------------------------------|------------------|
| Induction dose of propofol (mg) | 122.5 \pm 18.6 |
| Additional propofol (mg) | 10 (0 - 60) |
| Total dose of propofol (mg) | 142.1 \pm 28.1 |
| Baseline SBP (mmHg) | 125.6 \pm 16.1 |
| Baseline DBP (mmHg) | 76.2 \pm 11.9 |
| Baseline MAP (mmHg) | 90.3 \pm 13.1 |

SBP: Systolic blood pressure, DBP : Diastolic blood pressure, MAP : Mean arterial pressure.

DISCUSSION

The main finding of our study is that there is a significant association between the preoperative anxiety level and the post induction blood pressure fall after propofol use in adult female patients. However, not only the absolute change in blood pressure value, but also the percentage of blood pressure changes from baseline correlate with anxiety scores. After applying a logistic regression model to the possible confounding variables, such as patients' age, body weight, and dose of propofol, a significant association was found only between GAD-7 anxiety score and percent change in MAP and DBP, but not with percent change in SBP. The total dose of propofol was also found to be significantly associated with the percent change in MAP, which may be the main confounding factor in our study. Overall, a small to moderate change in blood pressure in the order 10-20 mmHg (Fig. 1 and 2) seen in otherwise healthy young female may not be clinically significant in our day to day anesthesia practice.

The most frequent adverse effect of propofol in anesthesia practice is hypotension. The decrease in sympathetic outflow is thought to be one of the causative factors of hypotension (12). Impairment of the baroreceptor-mediated reflex mechanism, direct relaxation of venous smooth muscles, and direct myocardial depressant effects may be other possible mechanisms (6-8). Even sedation doses of propofol cause a significant inhibition of the sympathetic system, resulting in hypotension in human adult volunteers (13). There has been evidence from a human study, that vasodilatation from propofol is also primarily mediated by sympatholysis, rather than a direct vascular effect (14). At this time, it is well known that preoperative anxiety increases sympathetic activity in humans (15). An increased sympathetic activity can be measured by various surrogate markers, such as skin conductance (16), baseline heart rate in pregnant patients (17), heart rate variability (18), positional blood pressure changes (19), and an increased sympathetic tone predicted post spinal anesthesia hypotension in cesarean section. So, we presumed that inhibition of sympathetic tone by an induction dose of propofol would cause an exaggerated fall in blood pressure in patients having a higher anxiety level.

For identification of anxiety in our patients, we used the GAD-7 score, which is an established tool for identification of generalized anxiety in primary care (20, 21). Along with GAD-7, we have used the VAS-A for assessment of preoperative anxiety too. VAS-A was found to correlate with Corah's Dental Anxiety Scale (CDAS), and Spielberger's State Trait Anxiety Inventory (STAI) in an observational study (22). It was found to be a useful tool for the assessment of preoperative anxiety in adult patients (23). In our study, we have also found a significant correlation between VAS-A and the GAD-7 scale.

Table 3
Correlation between the preoperative anxiety level (VAS-A and GAD-7 scale), change in blood pressure from baseline, and percentage of change in blood pressure from baseline (n = 100), Kendall's Tau-beta.

| | Δ SBP | Δ DBP | Δ MAP | % Δ SBP | % Δ DBP | % Δ MAP |
|-------|--------------------------------|--------------------------------|-------------------------------|--------------------------------|--------------------------------|-------------------------------|
| VAS-A | $\tau_b = 0.284$ p < 0.0001 | $\tau_b = -0.006$ p = 0.465 | $\tau_b = 0.099$ p = 0.092 | $\tau_b = 0.270$ p < 0.0001 | $\tau_b = -0.016$ p = 0.413 | $\tau_b = 0.107$ p = 0.071 |
| GAD-7 | $\tau_b = 0.281$ p < 0.0001 | $\tau_b = 0.144$ p = 0.022 | $\tau_b = 0.203$ p = 0.002 | $\tau_b = 0.273$ p < 0.0001 | $\tau_b = 0.115$ p = 0.052 | $\tau_b = 0.185$ p = 0.004 |

Δ SBP: maximum change in systolic blood pressure from baseline during the first 10 minutes, Δ DBP: maximum change in diastolic blood pressure from baseline during the first 10 minutes, Δ MAP: maximum change in mean arterial pressure from baseline during the first 10 minutes.

% Δ SBP: maximum percentage of change in systolic blood pressure from baseline during the first 10 minutes, % Δ DBP: maximum percentage of change in diastolic blood pressure from baseline during the first 10 minutes, % Δ MAP: maximum percentage of change in mean arterial pressure from baseline during the first 10 minutes.

LIMITATIONS

The most important limitation of our study is that we have not measured blood pressure invasively. Rather, we used non-invasive oscillometry for blood pressure measurement. Hence, there is a possibility that some amount of blood pressure variations during induction of general anesthesia were undetected. Second, the logistic regression model showed a significant association between GAD-7 and percent change in MAP and DBP, but not with SBP. This needs to be addressed in a separate study with a larger sample size and multicenter involvement. Third, we have included only female patients of relatively younger age groups. As it is already known that females have higher anxiety levels, it would not be legitimate to extrapolate our results to male patients and patients in other age groups. Last, in the multivariate analysis, we have found that the total induction dose of propofol has also affected the fall in blood pressure, which is a significant source of bias in our study.

CONCLUSION

We conclude that preoperative anxiety measured one day before surgery by simple scales such as VAS-A or GAD-7 correlates with hypotension in adult female patients following induction of general anesthesia with propofol. However, a dose-response of propofol causing hypotension cannot also be ruled out.

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