

PAIN

Preoperative anxiety and pain sensitivity are independent predictors of propofol and sevoflurane requirements in general anaesthesia

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Editor's key points

- Preoperative factors (e.g. anxiety, pain sensitivity) may impact on the perioperative period and long-term outcomes.
- Propofol doses correlated with state and trait anxieties dependent on anaesthetic depth.
- Postoperative pain was most strongly correlated with preoperative pain sensitivity, rather than anxiety.
- Identifying patients preoperatively who are likely to require higher anaesthetic and analgesic doses should aid individualized postoperative management.

Background. Psychological factors are thought to drive inter-patient variations in anaesthetic and analgesic requirements. This cross-sectional study investigated whether preoperative psychological factors can predict anaesthetic requirements and postoperative pain.

Methods. Before total thyroidectomy, 100 consecutive women completed the Spielberger's State-Trait Anxiety Inventory (STAI) and the pain sensitivity questionnaire (PSQ). Target-controlled propofol was administered for induction of anaesthesia, and sevoflurane-oxygen-air was given to maintain equal depths of anaesthesia, as determined by bispectral index (BIS) monitoring.

Results. Patients with higher anxiety scores (state and trait) required greater amounts of propofol to reach light (BIS=85) and moderate (BIS=75) levels of sedation, but only trait anxiety was significantly associated with propofol requirements in reaching a deep level of sedation (BIS=65). The MAC-hour of sevoflurane was significantly correlated only with PSQ scores. The postoperative pain intensity was significantly correlated with both STAI and PSQ.

Conclusions. Preoperative anxiety and pain sensitivity are independent predictors of propofol and sevoflurane requirements in general anaesthesia. Anaesthetic and analgesic doses could be modified based on the patient's preoperative anxiety and pain sensitivity.

Keywords: anaesthesia, general; anxiety; pain threshold; propofol, sevoflurane

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Psychological factors are thought to drive inter-patient variations in anaesthetic requirements and postoperative pain experiences, even for the same surgical procedure.^{1–4} The main psychological factors of interest in this area have been preoperative anxiety and pain sensitivity.^{5–7} Although many studies have assessed the effects of anxiety on perioperative variables such as haemodynamic changes and neuroendocrinological responses, pain, and analgesic requirements,^{5–9} less is known about the effects of pain sensitivity on intraoperative outcomes. In addition, studies showing associations between high levels of anxiety and

increased anaesthetic requirements have been of questionable scientific validity, were limited to only the hypnotic component of propofol-based anaesthesia, or failed to control anaesthetic depth during the surgical procedure, thus yielding inconsistent results.^{3, 10–12}

Before operation determined pain sensitivity has been shown to predict acute postoperative pain intensity, although this may also depend on the specific pain sensitivity test chosen.^{13, 14} Recently, Ruscheweyh and colleagues¹⁵ demonstrated that experimental pain intensity predicted by the pain sensitivity questionnaire (PSQ) was better than that by

pain-associated psychological factors. PSQ is an easy and safe self-rating instrument for non-invasive assessment of preoperative pain sensitivity by rating imaginable painful situations occurring in daily experiences.

We therefore evaluated whether increased preoperative anxiety and pain sensitivity are associated with (i) increased requirements for propofol to reach phased levels of sedation, (ii) increased requirements of sevoflurane to maintain an equal depth of anaesthesia, and (iii) increased postoperative pain intensity.

Methods

The study protocol was reviewed and approved by the Institutional Review Board of Yonsei University Health System Clinical Trial Center (Seoul, Republic of Korea) (IRB number: 4-2010-0117). It was registered with ClinicalTrials.gov (Registration Number: NCT01149239). All participants provided written informed consent. This cross-sectional study enrolled 100 consecutive women (ASA classification I) with euthyroid status undergoing elective total thyroidectomy. Patients with a history of psychiatric illness and those taking psychotropic medications, and also patients with neurological disorders or significant cardiovascular, respiratory, and hepatic diseases were excluded.

On the day of surgery, patient characteristic data were obtained from each patient's medical records. All patients fasted for at least 6 h before surgery and received no premedication. A 20 G i.v. cannula was inserted into a large antecubital vein and Ringer's lactate solution 10 ml kg⁻¹ was administered for 1 h. In an isolated calm preparing room, patients completed the Spielberger's State-Trait Anxiety Inventory (STAI)¹⁶ and PSQ.¹⁵ The investigators were blinded to the results during the study period.

In the operating theatre, patients underwent standard monitoring, with the bispectral index (BIS; BIS A-1050 Monitor®, Aspect Medical Systems, Newton, MA, USA) used to measure the depth of anaesthesia.¹⁷ To decrease artifacts, subjects were asked to close their eyes and not speak or move during the brief BIS assessment period. As BIS values are affected by noise disturbances, all non-attendant persons were asked to leave the room and any unnecessary lights were turned off.¹⁸

Heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), peripheral oxygen saturation (Sp_O₂), and BIS index were measured at baseline. All subjects were administered 5 litre min⁻¹ oxygen via a nasal probe to maintain Sp_O₂ above 95%. Using the Schneider pharmacokinetic model that runs on a microcomputer connected to an infusion pump (Fresenius Kabi Co., Orchestra Base Orima and DPS Module System, France), propofol 2% (Fresenius Kabi Co., Germany) was administered via a target-controlled infusion system to a preset target concentration of 2.5 µg ml⁻¹ until the patient reached the three desired levels of sedation, as determined by BIS indices of 85 (light sedation), 75 (moderate sedation), and 65 (deep sedation).¹⁹ If the BIS index did not reach the next, deeper level within 3 min, target

concentrations were increased by increments of 0.5 µg ml⁻¹. Propofol requirements to reach each BIS index were recorded. Positive pressure ventilation was available as required in the event of desaturation (Sp_O₂ < 90%). When a patient reached a BIS index of 65, the propofol infusion was stopped and positive ventilation was started. After tracheal intubation with fentanyl 1 µg kg⁻¹ and rocuronium 0.6 mg kg⁻¹, anaesthesia was maintained with sevoflurane in 50% oxygen-air at a flow rate of 4 ml min⁻¹. During surgery, sevoflurane concentration was adjusted to provide an equal depth of anaesthesia, as assessed by a BIS index of 40–50, while rocuronium was infused continuously at a rate of 10 mg kg⁻¹ min⁻¹ with additional doses when T1 of the train-of-four exceeded 15%. No other opioids were administered during surgery. The MAC-hour of sevoflurane was recorded.

Postoperative pain at rest was assessed by an independent investigator using a visual analogue pain score (VAS, 0–10) at 1, 24, and 48 h after surgery. Rescue fentanyl (0.5 µg kg⁻¹) was i.v. administered when postoperative pain VAS ≥ 5. The incidence rates of postoperative side-effects, including nausea, vomiting, pruritus, dizziness, and headache, were recorded and treated if necessary. Intra- and postoperative parameters were assessed by an independent anaesthesiologist blinded to assessments of preoperative anxiety and pain sensitivity.

The main association we examined was that between the amount of propofol required for induction of anaesthesia and the level of preoperative anxiety on the STAI. The number of patients required was based on previous results,³ which found that increased state anxiety ($r^2=0.285$, $P=0.006$) and trait anxiety ($r^2=0.233$, $P=0.146$) were predictors of propofol dose necessary for sedation. We calculated that a total of 95 patients were required with a two-tailed α value of 0.05 and a power of 80%. To control for protocol omissions, we enrolled 100 women. All data are expressed as mean (SD) or number of patients (%). Microsoft Excel version 10.1 (Microsoft Inc., Redmond, WA, USA) was used as a database for data collection and manipulation. All statistical analyses were performed with a statistical software package (SPSS/PC+; SPSS, Inc., Chicago, IL, USA). Normality was determined using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Linear regression analysis was used to determine whether STAI and PSQ scores were associated with propofol and sevoflurane requirements, and the association between psychological variables and postoperative pain intensity. A P -value of <0.05 was considered statistically significant.

Results

All patients successfully completed the STAI and PSQ. Patients' baseline characteristics, preoperative psychological variables, and intraoperative data are summarized in Table 1.

We found significant correlations between state and trait anxieties, whereas neither was associated with PSQ score (Fig. 1). Increased age was associated with lower PSQ

Table 1 Patient demographics and intraoperative characteristics. Data are expressed as mean (range) for age, or mean (sd). STAI, Spielberger's State-Trait Anxiety Inventory; PSQ, pain sensitivity questionnaire

Variables	
Demographics	
Age (yr)	47.2 (22–62.7)
Weight (kg)	58.2 (8.5)
Height (cm)	158.8 (5.5)
Preoperative psychological variables	
State-STAI	37.2 (11.9)
Trait-STAI	33.5 (12.2)
PSQ	75.1 (24.9)
Intraoperative data	
Duration of surgery (min)	89.9 (16.8)
Fluid administered (ml)	773.5 (160.9)
MAC-hour sevoflurane	1.6 (0.3)

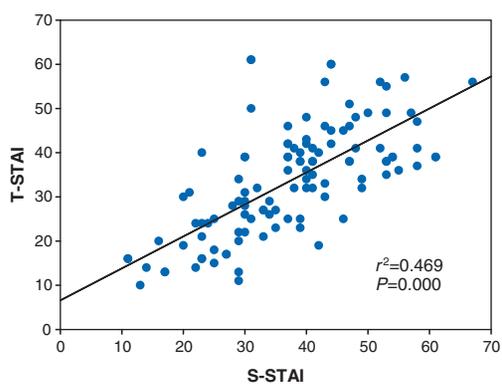


Fig 1 Correlations between state and trait anxieties and between each and pain sensitivity. STAI, Spielberger's State-Trait Anxiety Inventory; S-STAI, state anxiety; T-STAI, trait anxiety.

($r^2=0.152$, $P<0.001$). SAP correlated significantly with state and trait anxieties, and DAP correlated significantly with trait anxiety (Fig. 2). Pre-anaesthetic BIS values were not associated with STAI or PSQ.

During the induction of anaesthesia, patients with higher levels of state and trait anxieties required greater amounts of propofol to reach light (BIS 85) and moderate (BIS 75) levels of sedation (Fig. 3). The amount of propofol required to reach a deep level of sedation (BIS 65), however, was associated with higher levels of trait, but not state, anxiety. The amount of propofol in each level of sedation did not have any correlations with PSQ scores. The MAC-hour of sevoflurane was not significantly correlated with preoperative levels of state and trait anxieties, but was associated with PSQ score (Fig. 4).

When we assessed the relationship between psychological variables and postoperative pain intensity, we found that VAS 1 h after surgery was significantly correlated with

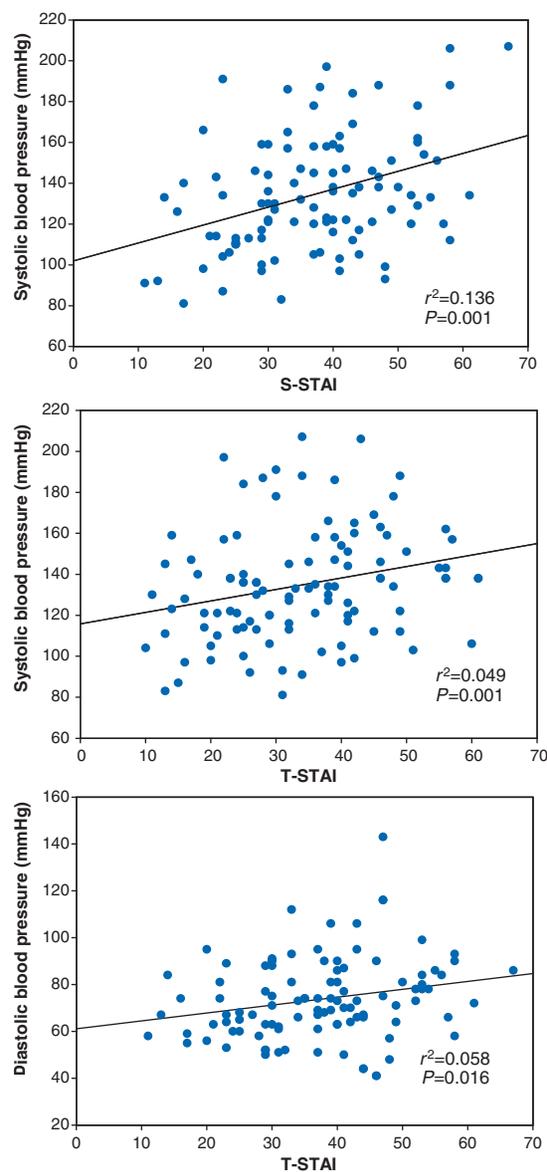


Fig 2 Correlations between anxieties and arterial pressures. STAI, Spielberger's State-Trait Anxiety Inventory; S-STAI, state anxiety; T-STAI, trait anxiety.

both STAI and PSQ scores. However, VAS 24 and 48 h after surgery were strongly correlated only with PSQ (Fig. 5).

During anaesthesia induction, one patient showed desaturation ($Sp_{O_2}<90\%$) at a BIS of 65. This patient was positively ventilated with 100% oxygen using a face mask, resulting in immediate recovery from desaturation. Postoperative adverse effects in our patients included nausea (20%), vomiting (4%), and mild fever (8%). All patients recovered after treatment with antiemetics and non-steroidal anti-inflammatory agents, as required, without any serious complications. None of these patients experienced any postoperative cardiovascular, pulmonary, or neurological complications during their hospital stay.

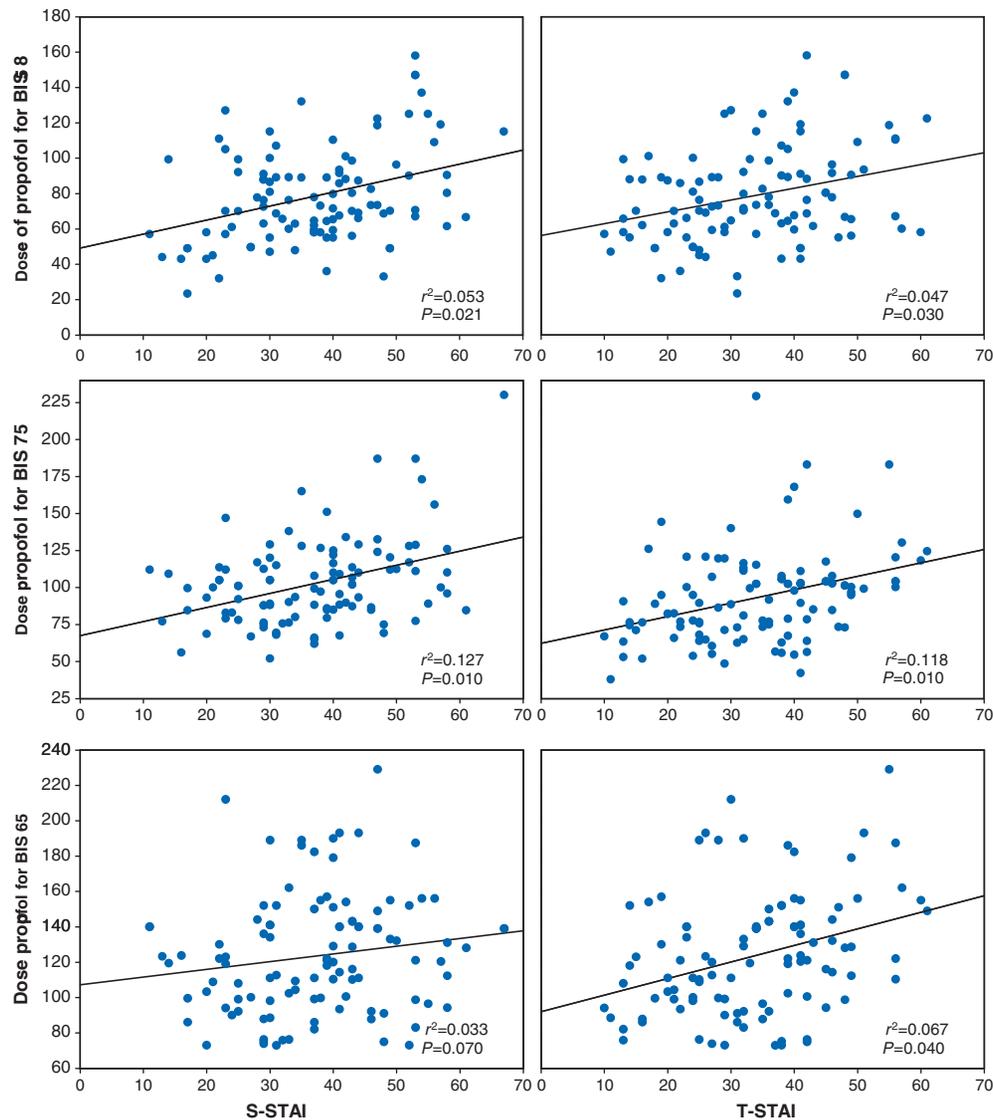


Fig 3 Correlations of psychological variables with propofol requirement by sedation level. STAI, Spielberger's State-Trait Anxiety Inventory; S-STAI, state anxiety; T-STAI, trait anxiety.

Discussion

Our findings confirmed that higher preoperative anxiety is correlated with increased propofol requirement in the induction of anaesthesia. Moreover, we found that individual pain sensitivity is a significant independent predictor of intraoperative sevoflurane requirement and postoperative pain intensity. To our knowledge, this study is the first to independently examine the effects of preoperative psychological variables on propofol requirements for induction of anaesthesia, on sevoflurane requirements for maintenance of anaesthesia, and on postoperative pain intensity in the same patient population.

Anxiety describes an unpleasant emotional state or condition. State anxiety is defined as subjective feelings of apprehension, nervousness, tension, and worry when

subjected to an anxiety-provoking stimulus, whereas trait anxiety is defined as individual differences in the disposition of responses to stressful situations. We found that state and trait anxieties were strongly correlated with each other, indicating that individuals with higher trait anxiety respond with increased state anxiety during an anxiety-provoking situation, such as surgery. In addition, people with high anxiety have increased subjective feelings of worry and apprehension, and more dramatic neuroendocrine responses to stimuli and increased cardiovascular activity.^{2 3 16} These might be important causes in more anxious patients of increased baseline haemodynamics and greater requirements for anaesthetics during surgery, although we did not measure the neuroendocrine responses of these patients.

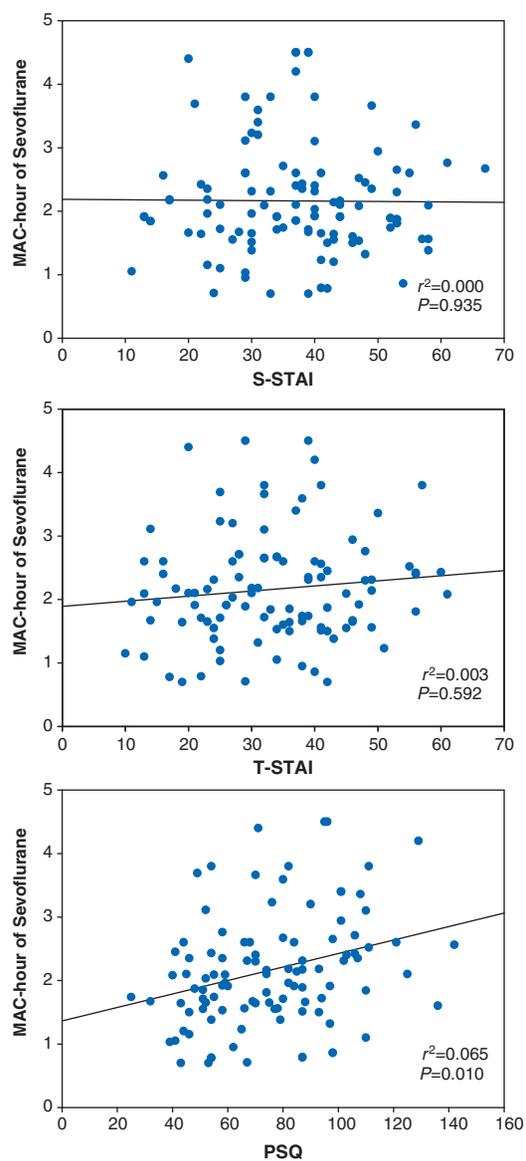


Fig 4 Correlations of psychological variables with sevoflurane requirement. STAI, Spielberger's State-Trait Anxiety Inventory; S-STAI, state anxiety; T-STAI, trait anxiety; PSQ, pain sensitivity questionnaire.

Previous studies have yielded contradictory results on the relationship between anxiety and requirements for anaesthetics. For example, some studies did not use validated measures to assess anxiety nor controlled for potentially confounding variables. In addition, many of these reports had common methodological limitation, in that they did not control for depth of anaesthesia, making determination of exact anaesthetic requirements difficult. Two clinical studies addressed this issue, but their results were not consistent, despite both using a BIS monitor during anaesthesia.^{3 20} The discrepancy between these two findings may be due to differences in technique and depth of anaesthesia.

We found that propofol requirements correlated with both state and trait anxieties during light-to-moderate levels of sedation, but correlated with trait anxiety only during deeper sedation.

Although psychological factors are related to pain, conflicting results have been observed. For example, some studies have reported that both state and trait anxieties were positively correlated with postoperative pain,²⁰ whereas others have reported a positive correlation between state, but not trait, anxiety and postoperative pain.^{13 21 22} Anxiety is associated with lower pain threshold,²³ overestimation of pain intensity,²⁴ and activation of the entorhinal cortex of the hippocampal formation.²⁵ Another study, however, did not find a significant correlation between anxiety and postoperative pain.²⁶ These discrepancies may be due to differences in questionnaires, types of surgery, and sample sizes. In contrast to studies reporting that anxiety was a major psychological predictor of postoperative pain,^{6 14} we found that postoperative pain intensity was predicted better by pain sensitivity than by anxiety. Indeed, we found that patients who experienced a higher level of preoperative anxiety were more likely to experience pain immediately after surgery but not for a longer period of time, with VAS at 24 and 48 h after surgery being strongly correlated with pain sensitivity.

Pain is a very complex, subjective, and emotional sensory experience, with both physiochemical and affective components. The pain experience is unique to any individual and has wide inter-individual variability. Preoperative experimental assessment of pain sensitivity has been shown to predict the level of acute postoperative pain.⁷ The PSQ has several advantages when compared with experimental pain intensity rating methods,¹⁵ including its rapidity (5–10 min), ease, and non-painful performance. Possible applications of the PSQ include the prediction of both acute postoperative pain and elevated pain sensitivity in individuals with a chronic pain disorder.^{20 27}

It has been shown previously that women may react to laboratory or psychosocial stressors with higher cardiovascular responses,^{28 29} but not always.^{30 31} Our data showed that preoperative arterial pressures correlated with anxiety scores, but HR did not. Noto and colleagues²⁹ demonstrated that mental arithmetic tasks significantly increased both state STAI and HR in women. Carrillo and colleagues³¹ reported gender differences in autonomic reactivity to public speaking and pointed to the sensitivity of electrodermal measures together with cardiovascular variables including finger pulse volume as indices of differences. But they did not find HR gender differences. These discrepancies may be attributed to differences in the subjects, timing and methods of assessing variables, and types of stressor. Small sample sizes might also have accounted for the mixed findings.

This study had several limitations. First, all measures used were based on subjective scorings of anxiety and pain rather than objective physical indicators. That is, a self-reporting bias (i.e. ranking anxiety as greater than the average person with a similar anxiety), rather than a causal

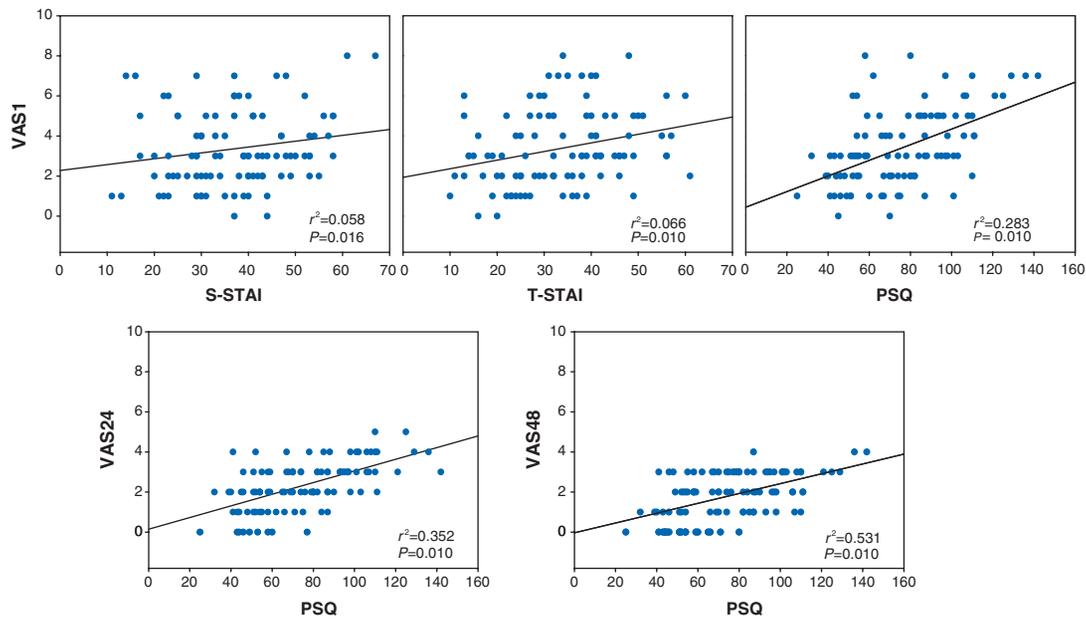


Fig 5 Correlations of psychological variables with postoperative pain intensity. STAI, Spielberger's State-Trait Anxiety Inventory; S-STAI, state anxiety; T-STAI, trait anxiety; PSQ, pain sensitivity questionnaire.

association, may have been responsible for the positive correlation between anxiety and induction of anaesthesia.³² Postoperative pain is very complex and may be influenced by many other factors. In addition, the clinical impact of our current results is limited, despite the statistical significance of the correlations. For most of the correlations, we observed between anxiety and anaesthesia, r^2 was below 20%, indicating that this model could not explain >70% of the variation. The advantage of our study, however, is that it provides additional support to results showing that preoperative anxiety and pain sensitivity were predictive of anaesthesia requirements, with significant linear relationships with intraoperative and postoperative outcomes.

Prediction of anaesthetic requirements in an individual patient may result in better tailored perioperative management and may improve patient outcomes. We suggest the modification of anaesthetic dose for general anaesthesia based on the individual patient's preoperative anxiety and pain sensitivity in female patients undergoing elective thyroidectomy.

Declaration of interest

None declared.

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