Increase of paradoxical excitement response during propofol-induced sedation in hazardous and harmful alcohol drinkers


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Editor’s key points

This study investigated the influence of chronic alcohol abuse on the incidence of paradoxical excitement during propofol sedation.

Paradoxical excitement occurred more frequently and severely in hazardous and harmful alcohol drinkers than in social drinkers during propofol-induced moderate-to-deep sedation, but not during light sedation.

Background. Paradoxical excitement response during sedation consists of loss of affective control and abnormal movements. Chronic alcohol abuse has been proposed as a predisposing factor despite lack of supporting evidence. Because alcohol and propofol have a common site of action, we postulated that paradoxical excitement responses during propofol-induced sedation occur more frequently in hazardous and harmful alcohol drinkers than in social or non-drinkers.

Methods. One hundred and ninety patients undergoing orthopaedic knee joint surgery were enrolled in this prospective and observational study. Subjects were divided into Group HD (hazardous and harmful drinkers) or Group NHD (no hazardous drinkers) according to the alcohol use disorder identification test (AUDIT). In study 1, propofol infusion was adjusted to achieve the bispectral index at 70–80 using target-controlled infusion. In study 2, the target concentration of propofol was fixed at 0.8 (study 2/Low) or 1.4 μg mL⁻¹ (study 2/High). Paradoxical excitement responses were categorized by intensity into mild, moderate, or severe.

Results. The overall incidence of paradoxical excitement response was higher in Group HD than in Group NHD in study 1 (71.4% vs 43.8%; P=0.022) and study 2/High (70.0% vs 34.5%; P=0.006) but not in study 2/Low. The incidence of moderate-to-severe response was significantly higher in Group HD of study 1 (28.6% vs 3.1%; P=0.0005) and study 2/High (23.3% vs 3.4%; P=0.029) with no difference in study 2/Low. Severe excitement response occurred only in Group HD of study 1 and study 2/High.

Conclusions. Paradoxical excitement occurred more frequently and severely in hazardous and harmful alcohol drinkers than in social drinkers during propofol-induced moderate-to-deep sedation, but not during light sedation.

Keywords: alcohol; anaesthetics i.v., propofol; paradoxical excitement; sedation

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Sedation is mandatory for relieving a patient’s anxiety and discomfort during most interventional or invasive procedures. Apart from their sedating action, sedatives and anaesthetics such as benzodiazepine, sevoflurane, or propofol could produce paradoxical excitement, in which patients show unexpected excitement of varying degree even at low doses.¹⁻³ These excitement responses to sedating agents include increased talkativeness, loss of cooperation, disorientation, excessive movement, sexual hallucinations, agitation, or rage.¹⁻¹⁰ The mechanism of this response is unknown, and so it is very difficult to predict which patients would show the excitement and its severity.

As for benzodiazepine, several factors have been suggested to predict the occurrence of paradoxical excitement during sedation, including personality of the individual, genetic predisposition, young or advanced age, degree of apprehensiveness of the patient, and chronic alcohol abuse.¹⁻³ ¹¹ ¹² However, supporting evidence for these factors is still lacking, in particular for chronic alcohol use-related problems during sedation with propofol.

Propofol is thought to have a similar mechanism of action as alcohol, in which the GABAₐ receptor is activated.¹³ ¹⁴ Given that the excitement response is induced by the pharmacological action of propofol, it can be postulated that the incidence and severity of the excitement response to propofol are in relation to alcohol use.

This study was performed to test the hypothesis that paradoxical excitement responses occur more frequently in hazardous and harmful alcohol drinkers than in social or non-drinkers.
Methods

This investigation was designed as a prospective study, and the protocol was approved by the Institutional Review Board of the authors-affiliated institute. Written consent was obtained from all patients or from legal guardians for those aged below 20.

Enrolled patients were 19–50 yr old with ASA physical status I–II and were undergoing elective knee joint surgery in the supine position under spinal anaesthesia. Exclusion criteria were (i) past or present use of hypnotics, anxiolytics, or other central nervous system-acting agents except alcohol, (ii) overt hepatic dysfunction, (iii) other illnesses involving cardiovascular, respiratory, or neurological systems, (iv) present or a history of hypersensitivity to propofol, and (v) combined trauma or injury other than the knee.

The alcohol use disorder identification test (AUDIT) was used to categorize subjects into two groups: hazardous or harmful drinkers (Group HD, score ≥8) and non-hazardous drinkers (Group SD, score <7). AUDIT has been known to be an effective and cost-efficient tool for identifying hazardous and harmful drinkers with high specificity and sensitivity.\(^1\)\(^1\)\(^5\)\(^1\)\(^6\) It consists of 10 questions on the frequency of alcohol consumption, alcohol-related problems, and dependence symptoms. Each question is scored from 0 to 4, with the sum of scores ranging from 0 to 40. A total score of 8 or more represents hazardous and harmful alcohol drinking. The frequency-volume test was also used to estimate the amount of alcohol consumption of patients over the past 3 months.

Spinal anaesthesia, sedation, and surgery

Patients were not given any premedication before anaesthesia. Spinal anaesthesia with 0.5% hyperbaric bupivacaine was performed in a routine manner, and the dosage of bupivacaine was chosen to attain the level of spinal block at T10 of sensory dermatome. Propofol was infused using target-controlled infusion (Master TCI infusion system, Fresenius-Vial, Brezins, France) after arterial pressure, heart rate, and level of spinal block had been stabilized. A pneumatic tourniquet of the thigh was inflated 15 min after the start of propofol infusion. Bispectral index (BIS) score was observed continuously using an Aspect A-2000 BIS monitor (Covidien, Mansfield, MA, USA) throughout the study period to assess the depth of sedation.

Paradoxical excitement responses

Paradoxical excitement responses were categorized with modification of cooperation score\(^2\)\(^7\) as follows: 0, none; no excitement response; 1, mild; increased talkativeness, irrational talking, or brief spontaneous movement with position remaining; 2, moderate; restlessness, loss of cooperation, or spontaneous movements requiring repositioning with no need of restraint; 3, severe; agitation and spontaneous movements with a need to restrain the patient. The response was observed for 30 min and scored every 5 min by one of the authors who was blind to the patient’s AUDIT score, and the highest score was used for statistical analysis. The observation period was limited to 30 min in both studies to eliminate a confounding factor caused by a different sedation time.

Study protocol

This investigation was performed in consecutive sessions (study 1 and study 2), and 190 patients (70 in study 1 and 120 in study 2) were enrolled.

In study 1 (Group HD=35, Group NHD=35), the infusion rate of propofol was controlled to maintain the BIS score in the range of 70–80. At the beginning of propofol administration, the target effect-site concentration of the infuser was set at 2.0 \(\mu\)g ml\(^{-1}\). After the BIS score decreased to 80, the target effect-site concentration was adjusted to achieve the target BIS score. In study 2, the effect-site concentration was fixed in the whole study time at 0.8 \(\mu\)g ml\(^{-1}\) (study 2/Low; Group HD=30, Group NHD=30) or 1.4 \(\mu\)g ml\(^{-1}\) (study 2/High; Group HD=30, Group NHD=30), but the other procedures and parameters were the same as in study 1.

Sample size was obtained using G*Power 3.1.2 by setting \(\alpha\) at 0.05 and power at 80%. In study 1, it was determined to detect a difference in the incidence of the paradoxical response between Group HD and Group NHD. The number of subjects needed in study 2 was calculated to detect a difference between study 2/High and study 2/Low in the incidence of moderate-to-severe response.

Statistical analysis

The results were analysed using SPSS software version 18.0.0 (SPSS, Chicago, IL, USA). Paradoxical excitement responses were analysed using \(\chi^2\) or Fisher’s exact test (two-sided in study 1 and one-sided in study 2). The overall incidence of paradoxical excitement response was analysed, and then subsequent analysis was performed to examine the differences in incidence of moderate and severe response that could be of clinical significance, in which categories of paradoxical response were grouped into two: no or mild vs moderate or severe. An independent \(t\)-test or \(\chi^2\) test was used for analysing other variables. Statistical significance was set at \(P<0.05\).

Results

Four patients of Group NHD were excluded from study 1 or study 2/High due to airway obstruction and hypoxia. One patient in Group HD was dropped from study 1 because of severe and uncontrollable behaviour, but the data of this patient were used for the analysis of paradoxical responses.

Patient characteristics, infused amount of propofol, and BIS score were not different between the groups in each study (Table 1). Laboratory data including aspartate aminotransferase, alanine aminotransferase, and mean corpuscular volume were not different between the two groups in both studies except for \(\gamma\)-glutamyltransferase, which was significantly higher in Group HD than in Group NHD (48.2 (35.5) vs 27.5 (17.6); \(P<0.001\)) and considered to reflect...
The overall incidence of paradoxical responses was significantly higher in Group HD than in Group NHD (71.4% vs 34.5%; Fisher’s exact test, \( P = 0.006 \)). A significantly higher incidence of Group HD than Group NHD (70.0% vs 34.5%; \( \chi^2 = 7.5; P = 0.006 \)) was found in study 2/High with an OR of 4.4 (95% CI: 1.5–13.2), but there was no difference between Group HD and Group NHD in study 2/Low. In contrast, no significant difference was observed in study 2/Low.

Discussion

Hazardous and harmful drinkers showed the paradoxical response more frequently and severely than social or non-drinkers in study 1 and study 2/High. In contrast, no significant difference was observed in study 2/Low.

Similar to previous reports in which chronic alcoholism or alcohol abuse was suggested as a risk factor for the paradoxical response,\(^3\) the result of the current study indicates that hazardous and harmful alcohol drinking is also one of the predicting factors for those responses. It seems that the manifestation of paradoxical responses to propofol observed in this study is not different from those to benzodiazepine seen in previous reports in which two distinctive manifestations of paradoxical excitement are disinhibited movement (such as abnormal body movement) and loss of affective control (such as increased talkativeness).\(^1\)\(^8\)

The incidence of paradoxical excitement response is unknown and greatly different among reports, ranging from 1% to 70%.\(^1\)\(^–\)\(^5\)\(^9\)\(^–\)\(^10\) This wide difference could be explained by the fact that there are no diagnostic criteria for paradoxical excitement responses, and the severity and type of responses are varied. A fairly high incidence of 45.1% (84/186) was observed in this study compared with that of the report on benzodiazepine. This is consistent with previous studies on propofol with an incidence ranging from 14% to 70%, although reports are relatively scarce.\(^2\)\(^4\)\(^17\)\(^20\) In addition, it might stem from the categorizing method used in the current study for the paradoxical response, in which even trivial responses, such as short irrational talking or brief spontaneous movement of the upper extremities, were counted as a mild paradoxical response. Of clinical importance, however, is the occurrence of severe paradoxical responses. It has been reported to be approximately in the range of 1–10%.\(^1\)\(^–\)\(^3\)\(^5\) Similarly, five patients (2.6%) showed severe excitement in this study, in which patients were trying to sit up or move their upper body. This is consistent with previous reports that severe paradoxical responses have occurred in approximately 2.6% of patients.\(^1\)\(^–\)\(^3\)\(^5\)
extremities so intensely that could hinder the anesthetic management and surgery. In addition, severe excitement was observed only in Group HD of study 1 and study 2/High. Several hypotheses and risk factors have been put forward to explain the mechanism of the paradoxical response to benzodiazepine, although it still remains unclear. It includes loss of cortical restraint, a central cholinergic effect, reduced serotonin neurotransmission, and genetic variability resulting from multiple allelic forms of the benzodiazepine receptors of GABA<sub>α</sub> channels. It is plausible that these could be involved in the paradoxical response to propofol because propofol also exerts its pharmacological action via GABA<sub>α</sub> receptors. In addition, excitatory changes in the EEG during anaesthesia induction with propofol were also found, which showed increased activity in the higher beta frequency bands with decreased activity in the slower frequency bands. However, the mechanism of this phenomenon has not been elucidated enough to explain the differences in excitement responses between hazardous and harmful drinkers and social or non-drinkers in this study.

One of the limitations of this study is related to classifying the paradoxical response. Without diagnostic criteria for the paradoxical response, the usual behaviour during sedation could have been regarded as paradoxical response, which resulted in over-estimation of the incidence of paradoxical responses even though moderate and severe response would represent the paradox.

This investigation demonstrates that hazardous and harmful alcohol use could be regarded as one of the risk factors for the development of paradoxical excitement responses during propofol-induced sedation. The risk is increased in moderate-to-deep sedation but not in light sedation. We suggest that care should be taken in the use of propofol for patients with hazardous and harmful alcohol use profiles, especially when the depth of sedation is increasing.

**Conflict of interest**

None declared.

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**References**