Use of Nitrous Oxide to Facilitate Induction for Electroconvulsive Therapy: A Case Report

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Conflict of interest: None declared

Patient: Female, 48-year-old
Final Diagnosis: Major depressive disorder
Symptoms: Depression and anxiety • loss of appetite • mania
Medication: —
Clinical Procedure: Electroconvulsive therapy
Specialty: Anesthesiology • Psychiatry

Objective: Unusual or unexpected effect of treatment

Background: The choice of pharmacologic agents used for electroconvulsive therapy (ECT) is critical as this can affect seizure duration and, ultimately, the effectiveness of ECT for the underlying condition. We report the use of nitrous oxide (N₂O) to sedate and place an intravenous (IV) catheter in a combative patient for the induction of anesthesia. We found no significant clinical effect on seizure duration while using N₂O in the pre- and intra-procedural period.

Case Report: We present the case of a 48-year-old woman with a history of major depressive disorder scheduled for electroconvulsive therapy (ECT). We used 50% nitrous oxide (N₂O) to sedate her and facilitate the placement of a 22-gauge IV catheter. When IV access was established, induction of anesthesia was done with 80 mg of methohexitol, which was later switched to 16 mg of etomidate and 80 mg of succinylcholine. After multiple ECT treatments, we observed no significant clinical effect on seizure duration while using N₂O when home medications were optimized. There is limited literature on the use of N₂O as a sedative agent in the perioperative period with other agents known to have no effect or beneficial effect on ECT treatments. We found no studies assessing the effect of N₂O on seizure duration.

Conclusions: Considering the pleasant odor, independent antidepressant activity, vasodilatory effect, low blood-gas partition coefficient, and minimal effect on respiration, N₂O may serve as the ideal adjunct to intravenous induction of anesthesia in an uncooperative or anxious patient. Further studies are warranted to confirm the efficacy and the safety of N₂O for use during ECT.

MeSH Keywords: Electroconvulsive Therapy • Nitrous Oxide • Receptors, N-Methyl-D-Aspartate

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Background

Electroconvulsive therapy (ECT) is a well-established treatment in the field of psychiatry for conditions such as treatment-resistant major depressive disorder, catatonia, mania, and schizophrenia. ECT involves an electrically induced seizure, ideally lasting more than 30 s. To induce a seizure, 70 to 120 volts of pulsed electricity is used unilaterally or bilaterally [1]. Anesthesia is provided during ECT for sedation and muscle relaxation. However, the choice of anesthetic agents for sedation is critical as it can affect the seizure quality, seizure duration, and post-procedure course. There is limited literature on use of nitrous oxide (N\textsubscript{2}O) as an adjunct anesthetic agent in the perioperative period for ECT.

We present the case of a 48-year-old woman with a history of major depressive disorder with severe psychotic (catatonic) features scheduled for ECT, in whom N\textsubscript{2}O was used to facilitate the placement of an intravenous catheter. We noted no significant decrease in seizure duration after optimizing the patient’s home and induction medications. This report adheres to the applicable EQUATOR guidelines and the Institutional Review Board (IRB) guidelines. HIPAA consent was obtained from the patient’s daughter to publish this case report.

Case Report

The patient was a 48-year-old woman with a history of mild cerebral palsy, postural orthostatic tachycardia syndrome, gastroesophageal reflux disease, and rheumatoid arthritis disease who presented with worsening symptoms of major depressive disorder. She was scheduled to undergo ECT sessions. Her home medications included lorazepam 0.5 mg 3 times a day and mirtazapine 7.5 mg daily. Before presenting to our hospital, the patient displayed symptoms of depression, loss of appetite, aggression towards others, trichotillomania, and self-harming behavior. Her symptoms were worsening over time and did not respond to oral medications. The results of testing for organic neuropsychiatric conditions such as autoimmune encephalitis and drug-related psychosis were negative.

The patient’s ECT treatments were performed using MECTA spectrum 5000 bilateral ECT with brief pulse. MECTA settings for the stimulus for all of the patient’s ECT treatments were the following: pulse width 1.0 meter per s, frequency 60 hertz, duration 6.0 s, and amplitude 0.8 meters. The initial seizure threshold was established by titration-threshold dosing. Motor seizure activity was observed, followed by seizure activity confirmed via EEG monitoring.

For her first 2 ECT sessions, physical restraints were required to obtain intravenous access, after which general anesthesia was induced with weight-based methohexital and succinylcholine. Due to the risks associated with bodily restraints, a decision was made to use N\textsubscript{2}O in her future sessions. A mask was used to deliver 50% N\textsubscript{2}O with 50% oxygen. A 22-gauge intravenous catheter was placed in the right hand as soon as adequate sedation was achieved. N\textsubscript{2}O was shut off, and 100% oxygen was used for the remainder of the procedure. We intravenously administered 80 mg of methohexital and 80 mg of succinylcholine for the procedure. The patient’s ventilation was managed with mask ventilation by the anesthesia provider.

The electroencephalogram (EEG) seizure duration lasted 28 s, which was shorter than her previous EEG seizure durations of 43 s and 37 s, respectively. For her fourth ECT, 16 mg of etomidate was used instead of methohexital. This treatment session resulted in an inadequate seizure duration of 26 s. Adequate seizure durations (>30 s) were obtained with subsequent ECT procedures after the discontinuation of her home medication, lorazepam. Based on the values in Table 1, N\textsubscript{2}O did not seem to have a clinically significant effect on EEG seizure duration when other medications and adjuvant anesthetic agents were optimized. With successive ECT treatments, the patient’s clinical and functional status greatly improved compared to pharmacologic therapy alone, as seen in Table 1. Prior to the patient’s initial treatment, she was nonverbal, uncooperative, and combative; however, after treatments 4–6, she began to speak in short sentences and was able to express herself. By treatments 10 and 11, she continued to be able to answer questions and by then was able to attend social events. Of note, care was provided by different anesthesia providers with varying levels of experience during each treatment, making it challenging to account for any differences in ventilatory strategy.

Discussion

Anesthetic agents such as muscle relaxants and anxiolytics were tried in the mid-1900s to mitigate some of the musculoskeletal and psychological complications associated with ECT [2,3]. Historically, 35% of patients have fractured vertebrae during ECT done without muscle relaxants. The adjuvant use of short-term paralytics such as succinylcholine by the anesthesia provider has greatly decreased fracture rates while simultaneously minimizing residual paralysis in the post-anesthesia care unit. In fact, Luccarelli, Henry, and McCoy noted a fracture rate of 3.56 per 1 million treatments in their study [4].

Over time, the drugs used have changed, and the complications due to ECT have decreased significantly. Among the commonly used anesthetic agents, propofol, lorazepam, and midazolam (oral and intranasal) decrease seizures and thus have little role in ECT [5–7]. Similarly, EMLA cream should not be used for pretreatment of myalgias as it can contain lidocaine,
Table 1. Summary of the 12 ECT treatments over 29 days with clinical and anesthetic details. MECTA spectrum 5000 bilateral ECT settings for the stimulus for all of the patient’s ECT treatments were the following: pulse width 1.0 meter per s, frequency 60 hertz, duration 6.0 seconds, and amplitude 0.8 meters.

| Rx No. | Day No. | Pre-procedure medications | Anesthetic | Paralytic | Static Imp. | Dynamic Imp. | Time of motor seizure | Time of EEG seizure | Pre ECT history from family |
|--------|---------|---------------------------|------------|-----------|-------------|---------------|----------------------|----------------------|-----------------------------|
| 1      | 1       | None                      | Methohexital 60 mg | Succinylcholine 60 mg | 590 | 189 | 22 | 43 | Nonverbal, non-compliant, attempting to bite |
| 2      | 3       | Acetaminophen 650 mg      | Methohexital 80 mg | Succinylcholine 80 mg | 620 | 179 | 22 | 37 | Nonverbal, eating and sleeping better |
| 3      | 5       | Acetaminophen 650 mg      | N₂O, Methohexital 80 mg | Succinylcholine 80 mg | 516 | 181 | 16 | 28 | Spoke a full sentence but uncooperative with ADLs |
| 4      | 7       | Acetaminophen 650 mg      | N₂O, Etomidate 16 mg | Succinylcholine 80 mg | 620 | 214 | 23 | 26 | Speaking in short sentences, Responds with gestures, gets out of bed, continues to stay uncooperative |
| 5      | 9       | Acetaminophen 650 mg      | N₂O, Etomidate 16 mg | Succinylcholine 80 mg | 620 | 219 | 26 | 35 | Up and walking around, eating well, minimal verbal communication, positive facial expressions, no reported A/V hallucinations |
| 6      | 12      | Acetaminophen 650 mg      | N₂O, Etomidate 16 mg | Succinylcholine 80 mg | 672 | 225 | 23 | 31 | More anxious and pacing around, broken sleep, eating well |
| 7      | 14      | Acetaminophen 650 mg      | N₂O, Etomidate 16 mg | Succinylcholine 80 mg | 1420 | 197 | 27 | 48 | Mostly nonverbal, appetite remains well. Not sleeping well at night. Not incontinent anymore and uses the restroom |
| 8      | 19      | Acetaminophen 650 mg      | N₂O, Etomidate 16 mg | Succinylcholine 80 mg | 550 | 170 | 16 | 22 | Spoke immediately after last Rx but decompensated to the point that she tried to run out of the house |
| 9      | 21      | Acetaminophen 650 mg      | N₂O, Etomidate 16 mg | Succinylcholine 80 mg | UK | UK | 26 | 47 | Incontinent again, nonverbal |
| 10     | 23      | Acetaminophen 650 mg      | N₂O, Etomidate 16 mg | Succinylcholine 80 mg | 620 | 236 | 23 | 41 | Patient answering questions, talking to family, went grocery shopping with family |
| 11     | 25      | Acetaminophen 650 mg      | N₂O, Etomidate 16 mg | Succinylcholine 80 mg | 700 | 222 | 22 | 32 | Attending social events, smiling and talking to people, less anxious, following commands to assist with exam |
| 12     | 29      | Acetaminophen 650 mg      | N₂O, Etomidate 16 mg | Succinylcholine 80 mg | 530 | 200 | 15 | 3 | |
an amide local anesthetic, which decreases seizure duration and inhibits the ability to achieve a therapeutic seizure. However, seizure duration is prolonged with etomidate [5–7]. Methohexital and remifentanil are short-acting agents that have been found to have no significant effect on seizure duration [5,6]. It should be noted that in our patient, the decision was made to switch from methohexital to etomidate during ECT treatment 4 because of unsatisfactory seizure duration. Methohexital is typically favored over etomidate as the first-line anesthetic agent for ECT because of its ability to blunt the hemodynamic response, whereas etomidate is associated with myoclonus and does not block the hypertension and tachycardia associated with ECT.

Dexmedetomidine has also been studied for use in ECT. Dexmedetomidine serves as an alpha-2 agonist. Because of its highly selective alpha-2 agonist effects, a recent study in 2017 found that dexmedetomidine at a rate of 0.2 μg/kg was beneficial in minimizing the sympathetic hyperdynamic response caused by ECT without altering seizure duration or delaying recovery [8]. Further, dexmedetomidine does not lead to respiratory depression, which is advantageous, particularly in patients for whom mask ventilation is difficult. It should be noted that it is possible that a more rapid infusion of dexmedetomidine can increase the risk of severe sinus bradycardia during anesthetic induction [8].

There are mixed reports on the effect of ketamine on seizure duration. N₂O and ketamine, however, are known to have an antidepressant activity of their own through affecting the N-methyl-D-aspartate (NMDA) receptor [6,9–11]. Because of the role of ketamine in acute reduction of depression severity, its role in ECT was recently studied as part of the KANCET randomized controlled trial. The KANCET trial found that there were no significant differences in any outcome measure during, at the end of, or 1 month following the ECT course, and that ketamine as an anesthetic does not enhance the efficacy of ECT [12].

Our literature search found that the use of N₂O during ECT has been documented as an adjunct maintenance agent with other agents that decrease seizure duration. However, we did not find any reports or studies on use of N₂O for ECT in the perioperative period with induction agents that are known to have no shortening effect on seizure duration. Considering the pleasant odor, independent antidepressant activity, calming psychological effect, low blood-gas partition coefficient, and minimal impact on respiration, N₂O needs to be investigated to confirm its acceptability and safety for use during ECT.

N₂O is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that confers an analgesic and anti-depressive effect to the gas. Sympathetic stimulation and release of endogenous opioids have also been reported to contribute to its antidepressant effects [13–15]. N₂O has a low blood-gas solubility coefficient of 0.42, with limited metabolism in the body, allowing its use in patients with renal and liver dysfunction without prolonging recovery times. Ketamine acts as an NMDA antagonist but is less favored due to its unpleasant hallucinogenic effects and sympathomimetic effect. A proof-of-concept study revealed a significant antidepressant effect but excluded patients undergoing ECT and patients with psychotic symptoms [15]. The inhibition of methionine synthetase by N₂O, a well-known side effect that results in elevated plasma homocysteine concentration and a decrease in B12 and folate levels, has not found to be clinically significant with repeated but short durations of exposure and can be managed by a folate-rich diet [16].

Finally, while volatile anesthetic agents such as sevoflurane have been shown to be adequate maintenance anesthetics for ECT, there have been no studies in the past decade to establish its widespread use in ECT. In comparison to nitrous oxide, sevoflurane would be less advantageous for several reasons. First, the time to induction and emergence of anesthesia would be longer due to its blood-gas partition coefficient of 0.65, which would argue against its use in a relatively short procedure like ECT [15]. Second, hypotension and arrhythmias are more pronounced with sevoflurane when compared to nitrous oxide [17].

**Conclusions**

Considering the above factors, we propose that N₂O may be useful as an anesthetic agent in patients with anxiety, symptoms of severe psychological disorders, history of difficult intravenous access, or needle phobia. Studies to evaluate the effect of N₂O on seizure duration, depression scores in conjunction with ECT, and perioperative adverse events are essential before expanding the use of N₂O.

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**Conflicts of interests**

None.
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