Patients' Physical Response to Thiopental and Alternative Anesthetic Agents in the Setting of Electroconvulsive Therapy

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INTRODUCTION

Drug shortages continue to be at the forefront of health care concerns.[1,2] Thiopental, an agent used for anesthesia during electroconvulsive therapy (ECT), became unavailable in North America in August 2010. The sole producer of this drug, Hospira (headquartered in Lake Forest, Illinois), ceased production because of liability concerns if thiopental were used via lethal injection to enforce the death penalty.[3] The thiopental shortage altered the practice of ECT, forcing a shift to alternative anesthetics. Of concern were the potentially negative consequences of using alternative agents, such as decreased efficacy and increased incidence of adverse effects.[2] This study examined ECT session outcomes, relative to recommended criteria for ECT (as described in Appendix 1), to compare patients' experiences during ECT performed with thiopental (the main anesthetic agent used in 2009) and their experiences during ECT performed with prescriber-selected alternatives used in 2011, when thiopental was in shortage.

METHODS

Study Population

The study population consisted of patients who underwent ECT at St Boniface Hospital or the Health Sciences Centre in Winnipeg, Manitoba, from January 1 to December 31, 2009 (when thiopental was available) or from January 1 to December 31, 2011 (when thiopental was not available). For the purposes of the study, ECT sessions were randomly selected from a master spreadsheet that listed, sequentially by date, each ECT session that occurred during each audit period. Each ECT session in each audit year was assigned a unique number, and a random-number generator was used to identify 75 treatment sessions to be audited in each period. Randomly selected treatment sessions were excluded at the point of initial data collection if the patient was less than 18 years of age, the selected session was a patient's first ECT session, or the patient's health records were inaccessible. This project was approved by the University of Manitoba Bannatyne Research Ethics Board, which also waived the need for informed consent.

Data Collection

A single investigator (K.G.) collected data from the patient records associated with the randomly selected ECT treatment sessions. A second investigator (D.M.M.W.) verified the completeness and accuracy of data collection and coding. Each patient's age, sex, diagnosis (according to the multiaxial diagnostic system of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition[4]), and classes of medications taken within 1 week before the ECT session were recorded. The collected data were compared with recommended criteria for an effective ECT session (see Appendix 1).

Anesthetic and adjunct agents given to the patient, ECT delivery parameters, and the duration of motor and electroencephalography seizures were recorded. Baseline vital signs (blood pressure, heart rate, and respiratory rate), as documented on the pre-ECT checklist, were collected and were compared with postprocedure results, as recorded in the recovery room.

The recovery room experience was evaluated in part by calculating the time spent there. Postprocedure adverse effects were obtained from the records of the recovery room. Where available, the duration of adverse effects and the rescue medication(s) administered were collected from the patient's medication administration record and integrated progress notes. The duration of adverse effects was defined as the difference between administration times for the last and first doses of rescue medication or the difference in times between when the adverse effect was documented to have begun and to have been relieved.

Data Analysis

Data were entered into a password-protected Microsoft Access database constructed for the project, and analysis was performed using Microsoft Access and Microsoft Excel software (Microsoft, Redmond, Washington).

The analysis focused on describing patients' demographic characteristics and their physical responses to ECT according to the anesthetic agent administered. ECT sessions were not analyzed according to audit year, as the audit periods were selected only to ensure a representative sample of ECT sessions during the period when thiopental was available and the period during which alternative agents were employed because of the shortage of thiopental.

RESULTS

Characteristics of Patients

The records for 150 ECT sessions were reviewed, of which 21 met one or more exclusion criteria. Data for 2 other sessions were also excluded: one session in which an unknown anesthetic was used and another session (involving propofol) for which the records contained insufficient information to contribute to the analysis. Of the 127 evaluable ECT sessions, 59 (46%) involved use of thiopental, 45 (35%) etomidate, and 23 (18%) ketamine (Table 1). The average age of the patients was similar in the 3 audit groups (range of means, 50.2–52.7 years). The ketamine group had the highest proportion of patients with cardiovascular disease (74% [17/23]) and the lowest proportion of patients with multiple indications for ECT (30% [7/23]). In contrast, 50 (85%) of the 59 patients in the thiopental group had more than one indication for ECT. The thiopental group had the lowest proportion of patients using benzodiazepines (19% [11/59]) and the highest proportion using atypical antipsychotics (73% [43/59]).

Characteristics of ECT Sessions

Most of the 127 ECT sessions (107 [84%]) were delivered bilaterally. In the majority of sessions (121 [95%]), the ECT stimulus parameters were as follows: pulse width 0.5 ms, frequency 60 Hz, and stimulus duration 6 s. For all patients, the current was 0.8 A.

Outcomes

Seizure Duration

Table 2 presents data for average duration of seizures (motor and electroencephalography) per session by anesthetic agent. In only 2 sessions (n = 1 each with etomidate and ketamine) was the duration of both motor and electroencephalography seizures within the intended targets (20–30 s [see Appendix 1]). The duration of electroencephalography seizure was excessive in 6 sessions (n = 4 with etomidate, n = 2 with ketamine); all other electroencephalography seizures were shorter than the intended duration. Among all treatment sessions in this retrospective analysis, 34% (43/127) involved patients who were receiving benzodiazepine therapy; however, in only 9% of those sessions

Table 1. Patient Population by Agent Received

Characteristic	Anesthetic Agent Received; No. (%) of Sessions*		
	Thiopental (n = 59)	Etomidate (n = 45)	Ketamine (n = 23)
Age (years) (mean ± SD)	52.4 ± 13.8	50.2 ± 11.7	52.7 ± 22.6
Sex, female	28 (47)	34 (76)	14 (61)
Concomitant medications			
Atypical antipsychotics	43 (73)	22 (49)	12 (52)
SSRIs	27 (46)	12 (27)	15 (65)
Benzodiazepines	11 (19)	23 (51)	9 (39)
Diagnosis (DSM IV)			
MDD	30 (51)	19 (42)	6 (26)
MDD with psychotic features	25 (42)	13 (29)	4 (17)
Cardiovascular disorder	28 (47)	18 (40)	17 (74)
Indication for ECT			
Resistant to treatment†	33 (56)	18 (40)	7 (30)
Severe depression	31 (53)	17 (38)	7 (30)
Depression with psychotic features	19 (32)	14 (31)	1 (4)
Prior response to ECT	17 (29)	19 (42)	5 (22)
Active or acute suicide risk	13 (22)	14 (31)	8 (35)
> 1 indication	50 (85)	25 (56)	7 (30)

DSM IV = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition[4];
ECT = electroconvulsive therapy; MDD = major depressive disorder; SD = standard deviation;
SSRI = selective serotonin reuptake inhibitor.
*Except where indicated otherwise.
†Resistant to initial treatment approaches, such as medication.

Table 2. Seizure Duration during Electroconvulsive Therapy Procedure

Anesthetic Agent	Mean Duration ± SD (s)	Seizure Duration; No. (%) of Sessions	
		< 20 s	> 30 s
Motor seizures*			
Thiopental (*n* = 57)	36.9 ± 11	4 (7)	33 (58)
Etomidate (*n* = 43)	39.1 ± 14	4 (9)	23 (53)
Ketamine (*n* = 23)	41.6 ± 15	1 (4)	16 (70)
EEG seizures*			
Thiopental (*n* = 56)	59.6 ± 28	1 (2)	44 (79)
Etomidate (*n* = 41)	75.7 ± 33	1 (2)	28 (68)
Ketamine (*n* = 23)	54.4 ± 19	0 (0)	20 (87)

EEG = electroencephalography, SD = standard deviation.
*Sum of *n* values is less than 127 because data were not available for some sessions.

(4/43) did the patient experience reduced duration of motor seizure, and none of these patients experienced duration of electroencephalography seizure less than 20 s. The ECT procedure delivered in all sessions aligned with ECT guidelines published in British Columbia.[5]

Adverse Effects

The average time spent in the recovery room was 39 min for patients who received thiopental, 35 min for those who received etomidate, and 42 min for those who received ketamine. Only 6 ECT sessions (*n* = 4 with thiopental, *n* = 2 with ketamine) met all postprocedure targets (as summarized in Appendix 1). For the other 121 sessions (95%), the patient was deemed to have experienced an adverse effect.

Table 3 presents the occurrence of adverse effects in the postanesthesia recovery room and the administration rates for prophylactic medications. Increases in blood pressure of at least 20 mm Hg from baseline occurred in 50 (39%) of the 127 ECT sessions (Table 3). Blood pressure differed (by at least 20 mm Hg in either direction) from target values for 58% (34/59 of the sessions involving thiopental, 40% (18/45) of those involving etomidate, and 43% (10/23) of those involving ketamine. All of the patients who had cardiovascular disease were also taking antihypertensive medications. Antihypertensive medications were given prophylactically in 16 ECT sessions (*n* = 12 with thiopental, *n* = 2 with etomidate, *n* = 2 with ketamine) (Table 3). Of the 12 ECT sessions involving thiopental in which antihypertensive medications were given prophylactically, 4 were marked by an increase in blood pressure of at least 20 mm Hg and 4 by a decrease in blood pressure of the same magnitude.

Post-ECT headache occurred following a high proportion of ECT sessions. The incidence of post-ECT headache was higher among those who received etomidate (58% [26/45]) than among those who received thiopental (47% [28/59]) or ketamine (39% [9/23]) (Table 3). Time to onset of post-ECT headache ranged from 20 to 374 min, and the duration of post-ECT headache ranged from 138 to 1208 min. Pre-ECT analgesia was given in a total of 12 sessions (*n* = 3 with thiopental, *n* = 9 with

Table 3. Adverse Effects and Prophylactic Medications Administered

Adverse Effect	Anesthetic Agent Administered; No. (%) of Sessions		
	Thiopental (*n* = 59)	Etomidate (*n* = 45)	Ketamine (*n* = 23)
Increase in BP			
Experienced increase in BP ≥ 20 mm Hg	25 (42)	15 (33)	10 (43)
Received prophylactic antihypertensives	12 (20)	2 (4)	2 (9)
Experienced increase in BP ≥ 20 mm Hg despite prophylactic antihypertensives	4 (33)	0 (0)	0 (0)
Headache			
Experienced headache after ECT	28 (47)	26 (58)	9 (39)
Received prophylactic analgesics	3 (5)	9 (20)	0 (0)
Experienced headache after ECT, despite prophylactic analgesics	1 (33)	7 (78)	0 (0)
Nausea			
Experienced nausea after ECT	3 (5)	4 (9)	7 (30)
Received prophylactic antinauseants	7 (12)	25 (56)	2 (9)
Experienced nausea after ECT, despite prophylactic antinauseants	1 (14)	3 (12)	0 (0)

BP = blood pressure, ECT = electroconvulsive therapy.

etomidate). In 8 (67%) of these sessions, the patients (n = 1 who received thiopental, n = 7 who received etomidate) went on to experience headache despite pretreatment with analgesic medication (Table 3).

Nausea was a less common post-ECT adverse effect. Use of ketamine was associated with the highest incidence of nausea (30% [7/23]); none of these patients received prophylactic treatment with an antinauseant. Pre-ECT antinausea medications were administered in 34 sessions (n = 7 with thiopental, n = 25 with etomidate, n = 2 with ketamine). Only 4 of these patients went on to experience post-ECT nausea (n = 1 with thiopental, n = 3 with etomidate). Vomiting, pain at the injection site, and myoclonic movements were infrequent. Patient agitation in the recovery room was documented with all agents (thiopental 12% [7/59], etomidate 18% [8/45], ketamine 9% [2/23]). Midazolam was administered as a rescue treatment in 8 (47%) of the 17 sessions in which patients experienced agitation following ECT.

DISCUSSION

Thiopental has long been considered the first-line anesthetic for ECT procedures. Extensive literature has evaluated alternative anesthetic agents, including etomidate, propofol, and ketamine, in the ECT setting; however, no agent has been clearly favoured as a first-line alternative to thiopental.[6-8] Previous studies showed no difference in efficacy of ECT with different anesthetics. The retrospective analysis of ECT in the current study showed that etomidate and ketamine were prescribed most often when thiopental became unavailable. In this study, the most common indication for ECT was severe depression, consistent with previous reports.[9]

The participants in this study typically continued their psychiatric medications throughout ECT treatment, but the psychiatric medications differed for each group (Table 1). Clear guidelines are not available for concurrent use of antidepressants or antipsychotics in the setting of ECT, and continued use is generally recommended.[5,10]

Variation in seizure duration was influenced by the anesthetic agent chosen and by unavoidable variability among patients. Many patients were also taking benzodiazepines, a class of drug that increases the seizure threshold and may decrease the efficacy of ECT therapy.[11,12] Literature on the use of oral benzodiazepines in conjunction with ECT is often contradictory, with confounding by many factors such as administration time, dose, half-life, active metabolites, and lipid solubility of the agent.[12] Given the data collected here, it is unclear whether use of benzodiazepines influenced seizure duration and ECT efficacy. However, most of the patients who were taking benzodiazepines did not receive them on the morning of the ECT (consistent with current recommendations[5,10]), and a clear association was not observed between receipt of benzodiazepines and reduction in seizure duration; as such, the influence of benzodiazepines upon ECT treatment and its outcomes may be minimal.[10]

Unexpectedly, only 2 sessions met targets for seizure duration. Target durations for electroencephalography and motor seizures (20–30 s) have been assigned arbitrarily in the past.[13] Although these targets are commonly used in clinical practice, there is considerable debate surrounding the relationship between seizure duration and clinical benefit.[13,14] Only one study found a positive correlation between seizure duration and therapeutic outcome,[15] and many other investigators have failed to identify such a relationship.[8,13,14] In the absence of formal, internationally accepted guidelines defining targets for duration of ECT seizures, this study used targets recommended by psychiatrist mentors for the project and by the American Psychiatric Association[10] and the British Columbia guidelines.[5]

Target length of stay in the recovery room is 15–20 min, but in this study, the mean length of stay in postanesthesia care was longer than 15 min for all 3 groups of patients. This similarity in deviation from the target may have been influenced by specific monitoring procedures at the health facility where these patients were treated.

This audit revealed that ECT was associated with adverse effects, most of which were minor, in almost all sessions (95%). Post-ECT headache prevailed in all groups. The effectiveness of prophylaxis to reduce the incidence of post-ECT headache is currently unknown, and there are few published studies of high quality.[16-19] In the current review, a low proportion of patients (9%) received pre-ECT prophylaxis for headache, and there was no consistent pattern in the drug selected for prophylaxis. Two-thirds of these patients went on to experience post-ECT headache, despite prophylactic medication. Evaluation of prophylactic agents for headache would be an area for future study, because of the prevalence and troublesome nature of this adverse effect among patients undergoing ECT.

Nausea occurred in a very small proportion of ECT sessions, most often those involving ketamine. Concomitant prophylactic antinausea treatment was administered in 25 (56%) of the 45 sessions involving etomidate, and only 3 (12%) of these patients went on to experience nausea. In contrast, prophylactic antinausea therapy was given in only 2 (9%) of 23 sessions that involved ketamine and 7 (12%) of the 59 sessions involving thiopental, following which only 1 patient (in the thiopental group) experienced nausea. These data support the suggestion that there may be a role for prophylactic antinausea therapy for patients undergoing ECT.

The findings of this study are limited by its retrospective nature and the fact that only a small sample of patient experiences was explored. The study was not designed to evaluate many of the parameters associated with ECT efficacy, such as electroencephalography patterns and post-ictal suppression, because those parameters are documented subjectively and inconsistently.[5,12]

This study documented utilization of alternative anesthetic agents following discontinuation of thiopental. The resultant small sample size for each anesthetic agent precluded statistical analysis comparing patient characteristics, ECT delivery parameters, and ECT procedure outcomes among the study groups. The weight-based dose of anesthetic was not documented and was therefore unavailable for analysis. The duration of adverse effects was calculated on the basis of subjective documentation, and the subjectivity of the data used might have led to overestimation of the duration of adverse effects.

CONCLUSIONS

Headache was a common adverse effect of ECT, regardless of the anesthetic used, and pretreatment with analgesics appeared to have little benefit. Nausea, although less common, was mostly seen with ketamine, and pretreatment appeared effective in the small group analyzed here. This review suggests that patients' physical responses to alternative anesthetic agents (etomidate or ketamine) for ECT were within the range of physical responses that occurred when thiopental was used. Despite its limitations, this review provides some reassurance to health care professionals that the anesthetic agents used when thiopental became unavailable were adequate in terms of safety and anesthetic efficacy.

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Appendix 1. Criteria for Effective Electroconvulsive Therapy

Criterion	Target
During procedure	
Seizure duration (motor and/or EEG)	20–30 s[1,2] Note: Seizures < 15 s are considered inadequate[1,2]; seizures > 2 min require intervention to halt them.[2]
Post-ictal suppression	10–20 s Note: Consensus opinion indicates that marked post-ictal suppression is desirable[1]; however, this is often documented with subjective, nonvalidated rating scales.[2]
Peak heart rate	140–180 beats/min[2]
Repeat electrical dose required	No
Repeat anesthetic dose required	No
Duration of procedure	15–20 min[3]
After procedure	
Blood pressure	Baseline ± 20 mm Hg SBP or DBP
Heart rate	Baseline ± 20 beats/min
Respiratory rate	Baseline ± 5 breaths/min
Oxygen saturation	95%–100%[3]
Nausea	None
Vomiting	None
Headache	None or minimal (lasting < 15 min)
Myoclonic movements	None
Irritation or pain at the injection site	None
Time in recovery room	15–20 min[2]

DBP = diastolic blood pressure, EEG = electroencephalography, SBP = systolic blood pressure.

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