THE ROLE OF CLINICAL PHARMACOLOGY AND PHARMACOGENETICS IN ELECTROCONVULSIVE THERAPY FROM SAFETY TO EFFICACY

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The research presented in this thesis was performed at the Departments of Clinical Pharmacy and Toxicology of Leiden University Medical Center, Leiden, The Netherlands and Anesthesia, Critical Care and Pain Medicine of Massachusetts General Hospital, Boston, Massachusetts, United States.

Financial support for the publication of this thesis was provided by AZL Onderzoeks- en Ontwikkelingskrediet Apotheek.

Cover design	Midas Mentink, Midas.Mentink.nl
Layout	Mentink, Midas.Mentink.nl
Printed by	Gildeprint, Enschede
ISBN/EVA	978-94-92026-08-8

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Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op donderdag 14 januari 2016
klokke 16:15 uur

door

Hooman Mirzakhani, M.D., MMSc.

geboren te Tehran
in 1970

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CONTENTS

Chapter 1	General Introduction	11
Chapter 2	Neuromuscular blocking agents for electroconvulsive therapy: A systematic review.	17
Chapter 3	Optimal Doses of Succinylcholine and Rocuronium during Electroconvulsive Therapy: A prospective, randomized, crossover trial	41
Chapter 4	Pharmacokinetics and Pharmacodynamics of Succinylcholine and Rocuronium during Electroconvulsive Therapy.	63
Chapter 5	Pharmacogenetics in Electroconvulsive Therapy and Adjunctive Medications.	83
Chapter 6	CYP2D6 metabolizer phenotypes in patients undergoing ECT after antidepressant therapy.	113
Chapter 7	Profound hypotension after anesthetic induction with propofol in patients treated with rifampin.	129
Chapter 8	Severe postoperative hemodynamic events after spinal anesthesia : a prospective observational study.	141
Chapter 9	General discussion and future directions	155
Appendices	Summary	174
	Samenvatting	178
	Dankwoord	181
	About the author	182
	List of publications	183

“It’s not that I’m so smart, it’s just that I stay with problems longer.”
Albert Einstein

(1879-1955)

1

General introduction

Electroconvulsive therapy (ECT) is an effective treatment in patients with acute and chronic psychiatric disorders resistant to psychotropic medications or need urgent control of their symptoms. Worldwide, it has been estimated that about one million patients receive ECT annually.[1,2] The aim of ECT is to induce a therapeutic tonic seizure with the minimum required energy, tailored to the condition of each patient. ECT has evolved into a widely recognized treatment modality in the practice of psychiatry.

While the efficacy ECT is mainly inherent to the biological alterations in brain through the induced therapeutic seizure, ECT procedural safety is pivotal to the outcome of treatment such that optimizing the procedural safety will improve the efficacy of the therapy outcome. An effective ECT procedure requires a good knowledge of anesthetic principles, understanding of the interaction between anesthetic drugs and seizure activity, the effect of anesthetic drugs on the ECT response and the clinical pharmacologic effects of the drugs used to attenuate the side effects related to ECT, and an awareness of the physiologic responses to the electrical stimulus. Additionally, it has been shown that some anesthetic drugs could augment the response to treatment or affect the quality of seizure that might be associated with short or long term efficacy of ECT.

Pharmacogenetics is the science to investigate an individual's sensitivity and response to a variety of drugs or the outcome after therapeutic intervention via studying genetic variations and gene-gene interactions.[3] Clinical insights into pharmacogenetics of ECT and understanding the biological mechanism of ECT not only improves its safety and efficacy in the patients, but also helps to develop alternative and more effective therapeutic agents in psychiatric disorders. This required knowledge also includes the adjunctive medications that might augment the response to treatment and can help to improve the efficacy of treatment in patients who do not respond to antidepressants or other psychotropic medication.

Therefore, the aim of this dissertation is to investigate the "safety and efficacy" of ECT, the two integrated aspects of this therapy procedure and how conducting investigations on these two indispensable precepts might lead to improving the quality of ECT outcome for treatment of indicated disease. To achieve this objective, we firstly explore the literature on the history of ECT application as a therapeutic procedure for psychiatric disorders and how the anesthetics, particularly invention of neuromuscular blocking agents (NMBAs) for ECT, improved the safety of this procedure (*chapter two*). Anesthesia for ECT includes the use of an induction agent and short acting muscle relaxant such as succinylcholine to minimize the amount of muscle contraction that occurs with the seizure. Accordingly, in *chapter two*, we also provide a comprehensive review on the neuromuscular blocking agent usage in ECT, their applied doses and potential side effects. Furthermore, we attempt to find supportive evidences on the suggestive NMBA 'rocuronium' as an alternative NMBA for choline that has

mainly been used for ECT due to its rapid onset time and short duration of action. [4]

In *chapter three*, a crossover randomized trial is designed to compare the commonly used muscle relaxant i.e. succinylcholine with rocuronium during the ECT and define the optimal doses that could predict the acceptable seizure induced muscle activity. The optimal doses for rocuronium and succinylcholine are defined and recovery time indices are explored. This research is distinguished as the first study, which identifies the optimal (minimal effective) doses of mostly used neuromuscular blockers in ECT using objective assessment by neuromuscular monitoring. The main objective of this investigation is providing a clinical guidance for clinicians in applying the minimal dose of succinylcholine or rcocuronium that could result in an optimized seizure activity during ECT.

Increasing our knowledge on pharmacology of succinylcholine and other nondepolarizing NMBAs in different conditions, i.e. simultaneous measurement of their plasma concentrations or a surrogate measure (pharmacokinetics) and neuromuscular blockade (pharmacodynamics) during ECT could help in increasing the safety of NMBA application or even the search for a new alternative NMBA. Pharmacokinetic–pharmacodynamic models help in measuring the drug effect and the relation between blood concentration and the target organ under the effect of drug. In *chapter four* and as a follow-up study on *the chapter three,* we conduct a PK-PD study to provide a quantitative model to describe the kinetics and the dynamics of succinylcholine chloride and rocuronium after the different bolus doses applied for inducing muscle relaxation in patients underwent ECT.

As earlier mentioned, inherent genetic differences and neurobiological alterations could be of high importance in response to ECT. In *chapter five,* we explore the past and current knowledge of pharmacogenetics in electroconvulsive therapy and adjunctive medications whose applications might augment the response to ECT and present the evidence of pharmacogenetics role in patients with psychiatric disorders undergone ECT. The safety of the procedure has two aspects: (i) safety of medications used during ECT (ii) side effects of ECT procedures e.g. cognitive disorders. In addition to reviewing these two aspects from pharmacogenetics perspective, we will also explore the functional genomics, gene polymorphisms and biological brain transmitters might play role in the effectiveness of ECT.

In spite of the availability of multiple pharmacologic classes of antidepressants (ADs) and their sequenced trials using available guidelines for depression treatment, majority of patients with unipolar or bipolar depressive disorders fail to achieve complete remission. [5] The enzyme cytochrome P450 2D6 (CYP2D6) plays an important role in the pharmacokinetics of many ADs (i.e. SSRIs and TCAs). Consequently, The *CYP2D6* gene could be a prominent contributor to interindividual drug response variability and predicted phenotype of enzymes

i.e. poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM) and ultrarapid metabolizer (UM).[6] In *chapter six***,** we investigate the accumulation of aberrant *CYP2D6* genotypes and predicted metabolizer phenotypes (UM, IM, and PM) potentially affecting the antidepressant treatment response in depressive patients indicated for ECT compared to patients with single episode of depression.

Anesthesiological care during ECT differs from the usual anesthesiological management for surgical patients [7,8] and a short acting hypnotic is used along with muscle relaxant. The ideal hypnotic agent for ECT has a short half-life, does not influence seizure duration and quality, and guarantees the patient's hemodynamic stability. Propofol has the shortest half-life of all the available hypnotic agents that makes it as the first choice hypnotic agent for induction of anesthesia for ECT. [9] Compared with methohexital, another hypnotic agent for ECT, propofol is associated with improved hemodynamic stability and an earlier return of cognitive function after ECT, though it might decrease the duration of seizure. [10] Although few side effects have reported after infusion of this hypnotic, it has increasingly been administered for general anesthesia and short procedures such as ECT in recent years. Therefore, clinicians should be attentive to any probable new side effect of propofol. The potential adverse effect of any drug could be due to either chemical structure of the drug (medication side effect) or an interaction with another drug (interaction side effect). In *chapter seven*, we investigate a new potential interaction side effect of propofol based on a series of reported occurrences of severe hypotension after induction with propofol in patients who had received rifampin for prophylaxis of infection for spinal surgery. We would like to focus on this not previously reported severe hypotension after induction with propofol in comparison to induction with other anesthetics and explore the literature for evidences that could support this observation.

In recent years, there has been substantial increase in the number of noninvasive and short procedural interventions that shorten patients' duration of stay at health care facilities. Consequently, healthcare practitioners are faced with a larger number of patients requiring procedural sedation. Effective sedation and analgesia during procedures not only provides relief of suffering, but also frequently facilitates the successful and timely completion of the procedure. However, any of the agents used for sedation and/or analgesia may result in adverse effects. [11] It has been reported that postoperative hemodynamic severe adverse events (PHASE), i.e. severe bradycardia and hypotension, can occur during recovery from spinal anesthesia. Incidence, contributing factors, and consequences of PHASE are unclear. In *chapter eight*, we aim to evaluate the incidence of PHASE, contributing factors and the impact on post anesthesia care unit (PACU) length of stay. Finally, in *chapter nine,* we will discuss the importance of the findings presented in this dissertation and the proposed future direction.

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2

Neuromuscular Blocking Agents for Electroconvulsive Therapy: A Systematic Review

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Acta Anaesthesiol Scand. 2012 Jan;56(1):3-16

ABSTRACT

Electroconvulsive therapy (ECT) is the transcutaneous application of small electrical stimuli to the brain to induce generalized seizures for the treatment of selected psychiatric disorders. The clinical indications for ECT as an effective therapeutic modality have been considerably expanded since its introduction. Anaesthesia and neuromuscular blocking agents (NMBAs) are required to ensure patients' safety during ECT. The optimal dose of muscle relaxant for ECT reduces muscle contractions without inducing complete paralysis. Slight residual motor convulsive activity is helpful in ascertaining that a seizure has occurred, while total paralysis prolongs the procedure unnecessarily. Suxamethonium is commonly used but nondepolarizing NMBAs are indicated in patients with certain comorbidities. In this review we summarize current concepts of NMBA management for ECT.

BACKGROUND

Electroconvulsive therapy (ECT) is a well-established psychiatric treatment; in which generalized seizures are induced by transcutaneous electrical stimuli to the brain. The aim of ECT is to induce seizure with the minimum required energy, tailored to the condition of each patient, to treat specific psychiatric disorders such as major depressive or cyclothymic disorders. ECT has evolved into a widely recognized, albeit controversial treatment modality in the practice of psychiatry. ECT is currently applied to between 5-10/100,000 persons/year in Asia and 20-100/100,000 persons/year in the Western Countries. In the United States approximately 4% of annual psychiatric admissions are solely for the purpose of ECT, [1] resulting in about 100,000 treatments per year. [2,3] In both the United Kingdom and Scandinavia, ECT appears to be declining in popularity, [4] and in other European countries its use remains highly variable. [5] As an example, ECT use is falling in Italy, but increasing in the Netherlands. [5] The reason for these differences in the application of ECT is not clear, but financial considerations may be a contributing factor. [6]

ECT owes its current acceptance to modern anaesthesia. Prior to the introduction of general anaesthesia, violent tonic-clonic convulsions associated with ECT could result in injuries such as limb fractures and compression fractures of vertebral bodies. The introduction of anaesthesia and neuromuscular transmission blockade to mitigate the tonic-clonic motor activity provided an effective means to reduce the physical and physiological trauma associated with uncontrolled tetanic muscle contractions.

Historical Perspective

Convulsive therapy for treatment of psychiatric disorders predates the use of electricity and the field of modern anaesthesiology. In the 1500s, the Swiss physician Paracelsus induced seizures by administering camphor by mouth to treat psychiatric illness. [7] The first report of the use of seizure induction to treat mania, using camphor was published in 1785. [7] Meduna advanced it based on the fact that patients with schizophrenia often improved when spontaneous epileptic seizures developed. [8] He induced convulsions in a patient in 1934 by injecting a solution of oleum camphoratum, which although successful, was subsequently replaced by metrazol. The result of metrazol therapy in schizophrenic patients was reported in 1935. In 1939, Bennett reported several cases of spontaneous fractures, which occurred during convulsions induced by metrazol. [8] He used Curare to modify metrazol-induced convulsive therapy. [9] The introduction of electric shock therapy by Bini and Cerletti (Italy) in 1939 [10] provided added impetus for the use of neuromuscular blockade. Bennett's technique of using curare to block neuromuscular transmission greatly reduced the incidence of fractures and dislocations due to contraction of skeletal muscles. [11,12] Electrical induction of

seizures soon replaced metrazol therapy because it was safer and had fewer adverse side effects. [13] The introduction of suxamethonium as a synthetic alternative to curare in 1951 led to the more widespread use of "modified" contemporary ECT. [11]

Contemporary use of ECT

ECT has become an increasingly important treatment for therapy-resistant major depression, which has a prevalence ranging between 3% in Japan to 17% in the US. In general, approximately 70 percent of all patients with major depressive disorder achieve remission with pharmacotherapy. [14] Patients who fail one or more adequate medication trials have a diminished but substantial rate of response to ECT. [15,16] ECT is highly effective in the elderly, perhaps even more so than the younger age groups.[17,18] ECT may also be used to treat bipolar disorder, mania and catatonia, neuroleptic malignant syndrome, Parkinson's disease, refractory epilepsy, Tourette syndrome and refractory obsessive compulsive disorder. [19,20]

The therapeutic tonic seizure that is induced by ECT usually lasts 10-15 seconds, and is followed by a clonic phase lasting 30-50 seconds, with a target seizure activity of more than 20 seconds. [21] Electroconvulsive therapy is commonly administered 2 or 3 times per week during the immediate course of treatment, until either improvement is seen or the treatment is deemed unsuccessful. [19] The total number of treatments administered during the short-term course of ECT varies, and is based on the presence or severity of cognitive side effects, as well as the efficacy of the treatment and evidence for clinical improvement.

Electroconvulsive Therapy and Neuromuscular Blocking Agents (NMBAs)

Bone fractures and dislocations have been reported when ECT treatments are performed without appropriate muscle paralysis. [22-24] Consequently, neuromuscular blockers are required to minimize the convulsive motor activity, in order to prevent fractures and physical injury during the seizure, [25-27] which is especially important in patients with osteoporosis or a history of spinal injury. [25,26] The aims of neuromuscular blocking for ECT could be summarized as: (1) Reduction of motor activity (with accurately assessed paralysis) to avoid injury, (2) Minimal interference with seizure activity, and (3) Prompt recovery of spontaneous ventilation without residual paralysis.

It is important to await the induction of general anaesthesia before neuromuscular blocking agents are administered. Although a relatively "light level" of anaesthesia is preferred (the procedure is not painful) to avoid prolonged emergence, the anaesthetic regimen should provide loss of response to vigorous stimulation while controlling the cardiovascular responses and autonomic arousal. [7,19] Cardiovascular responses consist of a brief initial increase in parasympathetic activity, followed by sympathetic response. In certain patients

the sequence described may result in bradycardia (or even sinus pause) followed by tachycardia, dysrhythmia, and hypertension. [28] If not properly controlled, the haemodynamic response to ECT can induce myocardial ischemia and even infarction, as well as transient neurologic ischemic deficits, intracerebral hemorrhages, and cortical blindness. However, adequate monitoring and therapy of hypertension and tachycardia with short-acting drugs enables ECT to be used even in patients with a variety of severe cardiovascular impairments. [29]

Based on its rapid onset, short duration of action, and rapid recovery,[30,31] suxamethonium is considered the NMBA of choice for ECT. Small doses of nondepolarizing NMBAs such as mivacurium and rocuronium are alternatives that may be used [19,28], but the prolonged effects of nondepolarizing NMBAs need to be adequately reversed before emergence from anaesthesia. Moreover, the sensitivity to the effects of these NMBAs is highly variable, even in patients with no known risk factors or complicating neuromuscular disorders. As an example, the coefficient of variation for the 50% effective dose (ED50) of rocuronium is > 25%. [32] Thus, even in a relatively small cohort of patients the ED50 may vary from 0.09 $mg.kg^{-1}$ to as high as 0.25 $mg.kg^{-1}$ (even higher in the absence of inhalational anaesthetics). Therefore, it is prudent to monitor the effects of nondepolarizing NMBAs during ECT.

Although 50% twitch depression is suggested to provide optimal conditions for endotracheal intubation, [33,34] this level of blockade may be insufficient to mitigate the excessive muscle contractions during ECT. A twitch depression of 11-25% was reported appropriate in one study [35], but the optimal level of neuromuscular blockade for ECT remains largely unknown. Future studies are warranted to systematically examine ECT quality and outcome with different levels of neuromuscular blockade, and to test if a twitch depression of 50% is also adequate for ECT.

Suxamethonium (Succinylcholine)

The mean dose of suxamethonium producing 95% blockade (ED_{95}) at the adductor pollicis muscle is 0.3 to 0.35 $mg.kg^{-1}$. The onset of skeletal muscle paralysis is achieved 30 to 60 seconds after administration of suxamethonium, and usually lasts between 5 to 10 min (5 min at the dose of 0.5 $mg.kg^{-1}$ and 10 min at the dose of 1 $mg.kg^{-1}$, assessed as 90% recovery from neuromuscular blockade). [36] Although a single best dose of suxamethonium has not been identified for ECT, 0.5 $mg.kg^{-1}$ to 1 $mg.kg^{-1}$ is often used based on previous experience of anaesthesia providers and defined interindividual variability of its effects. [1,27,36-45] Reducing the dose of suxamethonium from 1.0 to 0.60 $mg.kg^{-1}$ shortens the duration of neuromuscular effect at the adductor pollicis with 1.5-2 min. The extent to which this dose reduction affects the duration of neuromuscular blockade at the diaphragm, laryngeal adductors, or the upper

airway muscles in the ECT setting has not been studied. When complete neuromuscular block is important, however, doses of 1.0 to 1.5 mg.kg^{-1} are generally appropriate.[46] During the first ECT session, it has been recommended that a higher dose (1 mg.kg^{-1}) should be used [38,44], after which the suxamethonium dose can be adjusted based on the individual patient's amount of motor activity. [47] The time until full recovery is dose-dependent and reaches 10 to 12 min after a dose of 1 mg.kg^{-1}. [48] Using larger doses can lead to a complete absence of motor activity, which might impede monitoring of seizure adequacy.

Suxamethonium has many side effects, compelling the clinician to perform a risk-benefit analysis for individual patients prior to its administration. One of the most deleterious side effects of suxamethonium is hyperkalaemia leading to cardiovascular instability in susceptible patients. Several recent reports implicate distinct pathologic states that predispose a patient to suxamethonium-induced hyperkalaemia. [49-54] A common and important risk factor is prolonged immobilization, [55] especially in elderly patients. Concomitant presence of pathologic conditions that up-regulate the acetylcholine receptors (e.g. meningitis) can lead to a more rapid and profound increase in serum potassium levels after suxamethonium. [56] Other important side effects include bradycardia, [57] neuroleptic malignant syndrome (NMS) and malignant hyperthermia (MH). [36,57] Suxamethonium should, therefore, be avoided in any patient with a risk for severe hyperkalaemia [56] or with a history of, or susceptibility to NMS, MH, or catatonic schizophrenia. [58,59]

Irrespective of the choice of the anaesthetic technique, previous studies [60-63] have shown that ECT may produce asystole at any point during the course of a series of treatments. Conversely, even if haemodynamically significant bradyarrhythmias or asystole occur during one treatment, subsequent ECTs may be safely conducted if pertinent risk factors are eliminated (e.g. vagal tone or high potassium levels). [63]

Nondepolarizing Neuromuscular Blocking Agents

In contrast to suxamethonium, nondepolarizing NMBAs, used to achieve muscle relaxation for ECT treatment do not pose risk of side effects related to muscle fasciculation and cholinergic activation, or the potential to cause hyperkalaemia or malignant hyperthermia. The down-side of these NMBAs relates to their relatively long duration of action, typically beyond the time required for an ECT procedure, even when intermediate-acting NMBA are used. Also, there is wide variability in the sensitivity to the effects of these NMBAs, requiring that high doses be administered initially to reliably obtain neuromuscular blockade. The time to onset of effect is also variable between agents (see below) and need to be considered. Accordingly, adequate neuromuscular transmission monitoring is recommended to titrate the effect of these NMBAs, and pharmacological reversal is usually required.

Mivacurium

A nondepolarizing NMBA with a relatively short duration of action, mivacurium has been used as an alternative to suxamethonium for ECT treatment. [38,49,64-69] Savarese and collaborates showed that 0.08 mg.kg^{-1} of mivacurium (its ED_{95}) is less effective than 0.5 mg.kg^{-1} suxamethonium in blocking the neuromuscular transmission, when applied 120 seconds and 30 seconds before ECT, respectively. [70] Fredman and colleagues conducted a dose-effect study of mivacurium (0.12 to 0.2 mg.kg^{-1}) in a patient with susceptibility to neuroleptic malignant syndrome and history of prolonged bed-rest, and found that only 0.2 mg.kg^{-1} of mivacurium given 3 min before ECT was associated with effective muscle relaxation during ECT-induced seizure. The recommended dose of 0.15 mg.kg^{-1}, or any of the doses smaller than 0.2 mg.kg^{-1}, did not effectively mitigate the tonic-clonic response to ECT. [28,38] Although mivacurium can cause a significant histamine release and occasional hypotension,[27,71] the authors reported no haemodynamic instability or clinical signs of histamin release. [38] A similar dose (0.15-0.25 mg.kg^{-1}) appears to be sufficient for ECT in patients with myasthenia gravis, as was reported by Gitlin. [67] Others have reported optimal neuromuscular blockade with 0.12-0.16 mg.kg^{-1} (in a patient with neuroleptic malignant syndrome) [59] or 0.15-0.25 mg.kg^{-1} (patients with or without myasthenia gravis). [67] Based on data from three patients with major comorbidities (severe osteoporosis, amyotrophic lateral sclerosis, and bradycardia), Janis and colleagues recommended the use of 0.16 or 0.2 mg.kg^{-1} for ECT treatment. [66] A smaller dose (0.11 mg.kg^{-1}) was also reported to adequately blunt ECT-induced muscular contraction in a patient with post-polio syndrome with high risk of severe respiratory sequelae and neuromuscular dysfunction. [69] Mivacurium has been used as a substitute for suxamethonium to avoid (potential) adverse effects like hyperkalaemia or bradycardia. [64,65,68] (Table 2) Of note, mivacurium is also metabolised by pseudocholinesterase, and a prolonged effect is, therefore, expected in patients with pseudocholinesterase deficiency. Mivacurium usage in the United States has declined rapidly in favour of alternative agents that are perceived to offer a more rapid onset of action and a safer cardiovascular profile. It is more commonly used in Europe, in particular in the United Kingdom.

Atracurium and Cisatracurium

The dose of atracurium to effectively modify the tonic-clonic convulsions and prevent excessive muscle contractions during ECT was reported to be 0.5 mg.kg^{-1} (2.5 times its ED_{95}), given 2-3 min prior to the treatment.[52] [35] Given the profound neuromuscular blockade and the prolonged duration of action associated with this relatively high dose, nevertheless, Lui and colleagues examined if 0.3 mg.kg^{-1} also provides adequate neuromuscular blockade for ECT. The authors found that 0.3 mg.kg^{-1} was sufficient to keep the T1 blockade at 11-25%, whereas 0.5 mg.kg^{-1} maintained T1 blockade at 0-10% throughout the ECT. As was expected, the time to recovery to a T4 ratio of 0.5 was longer following 0.5 mg.kg^{-1} compared

with 0.3 mg.kg^{-1} of atracurium (9.2 ± 0.8 minutes vs. 4.3 ± 0.4 minutes). [35] Therefore, the authors recommended that the lower dose (0.3 mg.kg^{-1}) be used for ECT to reduce the risk for prolonged neuromuscular blockade and to ascertain the occurrence of generalized seizures, as indicated by peripheral muscle activity at the time of electrographic seizures.

In another report, 10-15 mg of atracurium was compared to 2-5 mg of suxamethonium in a 64 kg patient with atypical pseudocholinesterase. [72] The dose to produce 90 % first twitch blockade was reported as 15 and 2.5 mg for atracurium and suxamethonium, respectively. A dose of 0.5 mg.kg^{-1} of atracurium has been used in other reports in patients with cholinesterase deficiency or burn injury. [52,73] Because of the short duration of ECT relative to the duration of action of atracurium, reversal of neuromuscular blockade with a cholinesterase inhibitor is usually recommended. [27]

Cisatracurium, a stereoisomer of atracurium with minimal release of histamine, has largely replaced atracurium in clinical practice. At a dose of 0.05 mg.kg^{-1}, the time to 90% of peak effect is approximately 4.5 min, and the maximum effect (100%) is not achieved until 7 min after its administration. [74] Increasing the dose shortens the time to peak effect, but results in a long duration of action, which is usually unfavourable in a busy ECT setting. Despite an improved pharmacological profile with a reliable elimination, which is independent of renal or hepatic function, there are hitherto no clinical reports on the use of cisatracurium for ECT.

Vecuronium and Rocuronium

In appropriate doses, rocuronium has a speed of onset only marginally slower than that of suxamethonium, making it an appropriate alternative to suxamethonium for ECT. [75] Williams and colleagues employed 0.3 mg.kg^{-1} of rocuronium in a patient with delayed motor recovery caused by suxamethonium during a prior ECT treatment. [76] In a crossover study, Turkkal and colleagues compared rocuronium 0.3 mg.kg^{-1} versus suxamethonium 1 mg.kg^{-1} administered 90 seconds before ECT. The authors found similar ECT results in the two groups of subjects, with the exception of an increased time until the first spontaneous breath in the rocuronium group (9.46 vs. 8.07 min). Of note, the authors did not use quantitative methods to assess the neuromuscular transmission, limiting the ability to identify differences in the incidence and severity of residual paralysis. [75]

Dodson reported the effects of a 2 mg IV dose of vecuronium in a patient who had developed bronchospasm after induction of anaesthesia and administration of 30 mg suxamethonium. [77] The tonic-clonic response after vecuronium was similar to that after 30 mg of suxamethonium, and the authors concluded that 2 mg of vecuronium provides satisfactory neuromuscular blockade. Setoyama and colleagues administered vecuronium 0.01 mg.kg^{-1} followed

by a dose of 0.1 mg.kg^{-1} in three patients with NMS for ECT. They reported a prolonged anaesthesia time (38 vs. 19 min) in comparison to patients who received suxamethonium. [78]

Objective safety measures: Monitoring of the NMBA effect

Monitoring of the neuromuscular transmission during ECT is helpful in titrating the dose of the NMBA to the desired relaxation, and confirming its effect. The isolated arm or cuff technique[66,75] can be used to reliably monitor the motor response, particularly if electroencephalography (EEG) is not available to confirm the induction of generalized seizure activity. A forearm or leg is then isolated from circulation by inflating a blood pressure cuff to above systolic pressure after anaesthesia induction, but before NMBA administration. [79] The technique is, however, not widely applied, as the available data is inconsistent with respect to its clinical benefit. [80]

While the optimal relaxation level for ECT still needs to be defined in a prospective study, sufficient information is available on how to predict adequate recovery. If quantitative NMT monitoring (e.g. T1 recovery to 90% [81] or TOF ≥0.9 [59,66,68,72]) is not available, subjective methods such as visual and tactile assessment by a nerve stimulator, [82] eye opening, head lift, tongue depressor, [75,82,83] and hand grip should be considered (Table 1, 2). [84,85] However, recently published data confirms that subjective techniques for assessment of the NMT fail to detect mild but clinically significant postoperative residual curarization. [86-99] In fact, even very experienced observers are unable to manually detect TOF or double-burst stimulation (DBS) fade at TOF ratio of 0.4-0.6 or more. [100-103] Therefore, quantitative measurement of the TOF ratio using acceleromyography is increasingly recommended for titrating the dose of muscle relaxants and their antagonists, and for detection of residual paralysis. [33,90,96,99,104-113] Although the incidence of residual paralysis after ECT is unknown, recent data from postanaesthesia care units indicates an association between NMBAs and postprocedural residual paralysis as well as adverse respiratory events, and provides evidence in support of quantitative monitoring of the neuromuscular transmission. [99,114]

Reversal of the effects of nondepolarizing NMBA

Tables 1 and 2 summarize the studies and case reports that compare nondepolarizing NMBAs and suxamethonium in ECT treatment. As is evident from these studies and was also outlined previously in this review, the use of a nondepolarizing NMBA is often required as a substitute for suxamethonium in patients with different comorbidities. Given the relatively prolonged duration of action of the nondepolarizing agents, nevertheless, it is often recommended that clinicians monitor the neuromuscular transmission, and confirm the return of neuromuscular function before emergence from anaesthesia. [94,105,112,115-119] Cholinesterase inhibitors do not reverse deep levels of neuromuscular blockade, and may have undesirable autonomic side effects. [120] Their effect may also wear off before complete clearance of an NMBA, resulting

in recurarization with the risk for adverse respiratory events. [116,121] However, recurarization is unlikely after ECT, during which only a single and relatively low dose of an NMBA is given. A clinically interesting approach to neuromuscular blockade for ECT is to administer rocuronium for rapid onset of action, and to reverse the blockade with sugammadex.[81]

Potential role of Sugammadex for ECT

Given the limitations of anticholinesterases and the complications associated with residual neuromuscular blockade, new reversal agents have been investigated. The ideal reversal agent can be given at any time after the administration of a NMBA and completion of ECT, and is efficacious irrespective of the degree of neuromuscular blockade. It has ideally a rapid onset of action and a minimal side effect profile. [122,123]

Sugammadex is the first of a new class of selective muscle relaxant binding drugs developed for the rapid and complete reversal of neuromuscular blockade induced by rocuronium and vecuronium. Several studies have reported a predictable dose-response relationship with sugammadex for reversal of neuromuscular blockade. [124,125] Published data from Duvaldestin and colleagues suggest that 2 $mg.kg^{-1}$ sugammadex is sufficient to reverse rocuronium at a posttetanic count of 1 or 2. It has been extrapolated from these findings that doses as low as 1 $mg.kg^{-1}$ may provide clinically satisfactory reversal of rocuronium in <5 minutes once the TOF count has returned to a value of ≥2. [126] Available data from multiple other studies[104,111,127,128] support this hypothesis. [126] Sugammadex titration, using quantitative neuromuscular monitoring, may be a viable approach to optimizing the extent of neuromuscular blockade during ECT. Indeed, low-dose sugammadex (0.22 $mg.kg^{-1}$) can reverse a rocuronium-induced neuromuscular blockade at a TOF ratio of 0.5 within 2 minutes. [129] High-dose sugammadex, on the other hand, can reverse even high degree of neuromuscular blockade (T1=0), e.g. after a high dose of rocuronium. [81] Rapid reversal of deep blockade with high doses of sugammadex is appealing in a busy ECT setting but it may not be cost-effective. An insufficient dose of sugammadex, on the other hand, may result in incomplete decurarization, or potentially recurarization if multiple doses of rocuronium have been administered. [130] Although the efficiency and safety of the rocuronium-sugammadex combination for ECT needs further investigation, available data suggests that sugammadex, compared with neostigmine, may provide a safer reversal of moderate neuromuscular blockade. Low-dose sugammadex may also be cost-effective for the reversal of moderate or profound neuromuscular blockade, provided that the time saving factors reported in recent trials are taken into account. [131,132] Despite its use in Europe for many years, the American Food and Drug Administration have yet not approved sugammadex for clinical use for safety concerns.

Table 1

Conducted studies on use of NMBAs in ECT.

Study	Journal	Design	Subjects	NBMA	Dose	End point/measure	Frequency of ECTs	Outcome
Hoshi et al. (2011)[80]	J Anaesth	Crossover	Five patients (three Ms and two Fs) with mean age of 62.8 ± 5.9 years	Suxamethonium vs. rocuronium–sugammadex	0.1 mg/kg 0.6–16 mg/kg	T1 0% for ECT then on recovery T1 90%, time to T1 10% and 90%, seizure duration, time to first spontaneous breathing and eye opening	10 ECTs (three times per week at 1- or 2-day interval), first five ECTs with (S) then with rocuronium–sugammadex	Potential efficacy of rocuronium–sugammadex as an alternative to succinylcholine for muscle relaxation during ECT.
Turkkal et al. (2008)[74]	J Clin Anaesth	Crossover	13 patients, 18–60 years old	Rocuronium vs. suxamethonium	1 mg/kg 0.3 mg/kg	Motor seizure duration time, first spontaneous breath, head lift and tongue depressor test time, eye opening, Cuff technique	Modified ECT – three times per week, average of six to 12 ECT treatments	Rocuronium is an alternative to suxamethonium for ECT.
Rasmussen et al. (2008)[132]	J ECT	Clinical trial	36 patients (26–86 years old and eight men)	Suxamethonium	Variable doses used in facility	Convulsive movement, Strength of fasciculation, EEG seizure length, subjective report of myalgia	Unilateral, bifrontal, or bitemporal ECT – 189 treatments	Dose adjustment of (S) is unlikely to affect complains of myalgia.
White et al. (2006)[133]	Anaesth Analg	Parallel	20 patients: ECT = 10 vs. MST = 10; age, 49 ± 6 vs. 48 ± 4; weight, 84 ± 8 vs. 82 ± 10; M/F: 4/6	Suxamethonium vs. suxamethonium	97 ± 27 mg 38 ± 17 mg	Motor seizure, EEG seizure, Recovery time, Post-treatment Hamilton depression rating scale	ECT vs. MST/3–4 weeks and 10–12 for each	MST required lower dosage of NMBA usage and was associated with a more rapid recovery of cognitive function.
Kadar et al. (2002)[134]	Anaesth Analg	Parallel	50 obese patients in three classified group base on BMI (27,14,9)	Suxamethonium	40–120 mg Class I: 89 ± 25 Class II: 79 ± 14 Class III: 96 ± 17	Aspiration	Overall 660 ECTs (31,246,103)	Obese patient could be anaesthetised for ECT without full stomach ('aspiration') precautions.
Auriacombe et al. (2000)[135]	J ECT	Parallel	37 patients,18–86 years old; mean, 58.4, 29% M	Suxamethonium	0.7, 0.75, 0.85, and 0.89 mg/kg	Pre- and post-ECT agitation and serum lactate	245 bilateral ECTs/10 months	Increase of pre-ECT (S) dose prevented agitation in patients with increased serum lactate in ECTs.
Murali et al. (1999)[44]	Anaesth Analg	Crossover	100 referred patients; mean age, 27.9 ± 9.0, 31 Ms, two groups of 50 patients	Suxamethonium	0.5 mg/kg vs. 1 mg/kg	EEG & motor seizure duration, 5-point scale motor seizure modification, Time for 50% recovery of NM twitch height	Unilateral = 25; bilateral = 25–0.5 mg/kg groups 2–5; 0.1 mg/kg groups 2–4	The larger dose is more effective in modifying the peripheral convulsion.
Cheam et al. (1999)[136]	Can J Anaesth	Crossover	16 depressed otherwise healthy patients, aged 26–27, weight: 40–78 kg	Suxamethonium vs. mivacurium	0.5 mg/kg 0.08 mg/kg	Score of seizure activity, Duration of seizure, time to first breath, ability to protrude tongue and hand grip for 5 s	N/A	Seizure modification was better after low-dose suxamethonium than after low-dose mivacurium.
Lui et al. (1993)[35]	J Clin Anaesth	Parallel	24 patients in two groups of 12 each, 14 Ms, weight: 59 ± 3.2 vs. 62.7 ± 3.5	Atracurium	0.3 mg/kg IV vs. 0.5 mg/kg IV	EEG activity during seizure Duration of multiple-monitored ECT, Grading of tonic –colonic ECT-induced convulsion based on observation	Bilateral multiple-monitored ECT – total of each group ECT treatments: 36	Suggests lower dose of atracurium to ascertain the occurrence of ECT-induced seizures.
Konarzewski et al. (1988)[43]	Anaesthesia, abstract	Parallel	52 patients in three groups	Suxamethonium	50, 25, and 15 mg	N/A	N/A	Practical advantage of 25 mg over 50 mg, and theoretical advantage over 15 mg of suxamethonium.
Pitts et al. (1968)[40]	Arch Gen Psychiatry, abstract	N/A	N/A	Suxamethonium	N/A	N/A	500 ECTs	Modification of suxamethonium in ECT.

BMI, body mass index; ECT, electroconvulsive therapy; IV, intravenous; F, female; M, male; MST, magnetic seizure therapy; N/A, not available; NMBA, neuromuscular blocking agent.

Table 2

Case report on the use of NMBAs for ECT.

Author	Journal	Subjects	NBMA	Dose	Clinical report/measure	Frequency of modality	Author's conclusion
Batistaki et al. (2011)[137]	J ECT	26-year-old man, with catatonic schizophrenia and low pseudocholinesterase, height:180 cm; weight:85 kg	Rocuronium + sugammadex	0.4 mg/kg 2 mg/kg	TOF monitoring, bispectral index, time to first spontaneous breath, duration of seizure, recovery time to TOF = 1	Eight consecutive ECTs, every 48 h	Rocuronium used with thiopental and reversed with sugammadex can be a safe alternative for suxamethonium for ECT.
Bryson et al. (2011)[138]	J ECT	A 73-year-old, 72-kg man with bipolar disorder referred for ECT 12 days after the initiation of chemotherapy	Suxamethonium		Prolonged neuromuscular blockade during third ECT after chemotherapy, blood pressure cuff, tibial nerve stimulator (absence of motor response), seizure duration by ECG, and spontaneous recovery of diaphragmatic movement	10 bilateral ECTs over 8 weeks before chemotherapy. Six ECTs in 8 days after onset of new depression episode and chemotherapy	Drug induced acquired butyrylcholinesterase deficiency. With attention paid to subsequent (S) dose titration to effect, treatment continued uneventfully.
Waghmare et al. (2010)[139]	Gen Hosp Psychiatry	40-year-old male patient with organophosphorus poisoning	Suxamethonium	25 mg	Prolonged apnea	One ECT treatment, then nine unmodified sessions	Prolonged apnea because of organophosphorus poisoning.
Zisselman and Jaffe (2010)[50]	Am J Psychiatry	19-year-old woman with Torsade de Pointe during first ECT, weight: N/A	Suxamethonium vs. rocuronium	30 mg 15 mg	Absence of arrhythmia in subsequent eight ECTs	Bitemporal ECT – nine ECT treatments	Nondepolarising NMBAs as alternative to suxamethonium in case of risk of hyperkalaemia.
Birkenhager et al. (2010)[63]	J ECT	21-year-old man with schizophrenia	Suxamethonium vs. mivacurium	90 mg 12 mg	Bradycardia	Three ECTSs with (S), nine ECTs with mivacurium	Mivacurium usage in case of bradycardia.
Setoyama et al. (2009)[77]	Masui, abstract	Two schizophrenic and one depressive patient with neuroleptic malignant syndrome	Vecuronium vs. suxamethonium	Two times 0.01 mg/kg N/A	Anaesthesia time, no negative report of ECT procedures	Modified ECT – N/A	Vecuronium as an alternative in NMS.
Arias et al. (2009)[140]	J ECT	64-year-old white female	Suxamethonium	60 mg	Asystole, normal serum potassium, ECT (no change for hyperkalaemia)	Asystole in 13th ECT	Asystole because of molecular structure of (S) is unpredictable.
Williams et al. (2007)[75]	J ECT	67-year-old, 90-kg man with psuedocholinesterase deficiency, diagnosed in first ECT	Suxamethonium vs. rocuronium	80 mg 30 mg	Clinical and electrographic duration of seizure in first ECT	Right unilateral ECT – one (S) + four (R) ECT treatments	Suggestion of rocuronium as a substitute for ECT in psuedocholinesterase deficiency.
Holak et al. (2007)[62]	Can J Anaesth	73-year-old man with major depression and catatonia	Suxamethonium	1–1.5 mg/kg	Asystole, normal serum potassium	39 uneventful previous ECT treatments with asystole in 40th and safe subsequent ECTs	ECT may produce asystole at any point of procedure. Subsequent ECT may be safely conducted.

Table 2 Continued

Author	Journal	Subjects	NBMA	Dose	Clinical report/measure	Frequency of modality	Author's conclusion
Hudcova and Schumann (2006)[48]	Gen Hosp Psychiatry	34-year-old woman (BMI = 59 kg/m^2) with NMS, arrhythmia and K↑ in third ECT by (S)	Suxamethonium vs. atracurium and mivacurium	In third ECT 140 mg N/A	Serum potassium, recovery time	ECT with (S) until restoration of physical activity	Nondepolarising NMBAs may eliminate the need for suxamethonium use during ECT.
Prieto Martin et al. (2006)[141]	Rev Esp Anestesiol Reanim	35-year-old woman at 30 weeks' gestation	Suxamethonium	N/A	N/A	Nine sessions (three times/week)	Clinical improvement and safe labour within 2 days after ECT.
Ozer et al. (2005)[142]	J ECT	56-year-old woman with Parkinson's disease and neuroleptic malignant syndrome	N/A	N/A	Improvement of neuroleptic malignant syndrome, psychiatric and parkinson's symptoms	Bilateral ECT – five sessions, three times per week	ECT might be effective and life saving in severe, drug resistant cases of neuroleptic malignant syndrome.
Magid et al. (2005)[143]	J ECT	A man with recent myocardial infarction (10 days before ECT)	Suxamethonium	80–100 mg	N/A	Bilateral – seven ECT treatments	ECT could be safe in patient with recent myocardial infarction.
Calarge and Crowe (2004)[144]	Ann Clin Psychiatry, abstract	A patient with myasthenia gravis	N/A	N/A	N/A	N/A	ECT was done safely, with appropriate precautious.
Liu and Modell (2001)[68]	Anaesthesiology	64-year-old, 70-kg man with post-polio syndrome	Mivacurium	0.14 and 0.11 mg/kg	Neuromuscular response to electrical stimulation, duration of ECT	Four ECT treatments in 8 days	Mivacurium at a dose of 0.11 mg/kg was adequate in preventing muscle contraction.
Kadar et al. (2001)[145]	Anaesth Analg	51-year-old, 96-kg man, family history of MH to suxamethonium	Rapacuronium	75–70 to 65–60 mg 0.6–0.8 mg/kg	Observation of motor response to tetanic stimulation	Four sessions	Rapacuronium usage in a patient at risk for MH.
Nisijima and Ishiguro (1999)[146]	J ECT	Five cases of NMS	Suxamethonium	N/A	N/A	Bilateral – 17 ECTSs	ECT is a useful therapy for psychotic patients with NMS.
Trollor and Sachdev (1999)[147]	Aust N Z J Psychiatry	13 patients with NMS, weights: N/A	Suxamethonium vs. atracurium	0.5 mg/kg 20 mg	Temperature, creatine kinase	Bilateral and unilateral – three times/week	The use of atracurium was associated with a prolonged duration of anaesthesia.
Dillard and Webb (1999)[81]	AANA J	53-year-old man with suicide attempt by Dursban, weight: N/A	Suxamethonium	First ECT: 40 mg; second and third: 20 mg; third to sixth: 15 mg	Peripheral nerve stimulator, head lift Cholinesterase level	Seven ECTs/2 weeks, 10 ECTs/patient	Lower dose of (S) for ECT in organophosphate poisoning.
Cooper et al. (1999)[64]	Anaesthesiology	40-year-old white catatonic woman	Suxamethonium vs. mivacurium	120 mg N/A	Serum potassium↑ with suxamethonium in second, third, and fourth ECTs	Four ECT treatments with suxamethonium and then with mivacurium	Suggestion of a short-acting, nondepolarising NMBA for immobile catatonic patients.
Herriot et al. (1996)[148]	Br J Psychiatry	19-year-old, 54-kg woman with severe myalgia during her first two ECT treatments	Suxamethonium vs. vecuronium + suxamethonium	First and second ECT: 30 mg, 50 mg 1 mg before 50 mg of suxamethonium	Myalgia	At least four ECT treatments	Pretreatment with Vecuronium should be considered for ECT-induced muscle pain.

Janis et al. (1995)[65]	Can J Anaesth	64-, 69-, and 76-year-old men with osteoporosis, amyotrophic lateral sclerosis and cardiac arrhythmias	Mivacurium	0.2 and 0.16 mg/kg or 8 mg	Orbucularis oculi for TOF and peripheral nerve stimulator, isolated cuff to monitor seizure	Six ECT treatments over 13 days	Mivacurium should be used in elderly patients with comorbidities.
Jaksa and Palahniuk (1995)[57]	Anaesth Analg	25-year-old, 60-kg woman	d-tubucorare suxamethonium	3 mg 50 mg	Ventilation recovery, head lift, plasma cholinesterase↓	One ECT	Prolonged apnea because of organophosphate poisoning.
Fredman et al. (1994)[38]	Anaesth Analg	N/A A patient with neuroleptic malignant syndrome and prolonged bed rest	Suxamethonium Mivacurium	0.5–1 vs. 1.2–1.58 mg/kg 0.12, 0.15, 0.18, and 0.2 mg/kg	Twitch response to TOF stimulation	Over 6 month ECTs, four ECT treatments	Suxamethonium and mivacurium are more effective at higher doses.
Kelly and Brull (1994)[58]	Can J Anaesth	29-years-old, 49-kg woman with NMS because of neuroleptics	Suxamethonium vs. mivacurium	30 mg, 7 mg 0.12–0.16 mg/kg	Seizure duration on EEG, creatine kinase, and TOF for adductor pollicis	First two ECTs, then 10 ECTs in the next 4 weeks	Mivacurium is a suitable agent for patients with neuroleptic malignant syndrome undergoing ECT.
Gitlin et al. (1993)[66]	Anaesth Analg, abstract	Four patients, one with myasthenia gravis	Mivacurium	0.15–.25 mg/kg	N/A	N/A	N/A
Burnstein and Denny (1993)[67]	Anaesthesia	71-year-old female, with progressive cervical myelopathy, 50 kg	Mivacurium	6 and 5 mg	Bard nerve stimulator for TOF	Nine ECT treatments	Mivacurium is a satisfactory alternative to (S) for ECT if needed.
Swartz (1990)[149]	J Nerv Ment Dis	Five patients with post-ECT agitation	Suxamethonium	0.7 vs. 1 mg/kg	N/A	20 ECT with 0.7, then 15 sessions with 1.0 mg/kg	No agitation after the higher dose of suxamethonium is administered.
Stack et al. (1988)[72]	Br J Anaesth	76-year-old woman with plasma cholinesterase deficiency	Suxamethonium vs. atracurium	30 mg 10 and 15 mg	Apnea, peripheral nerve stimulator	One ECT by (S) and two ECTs by (A)	Atracurium as a substitute for (S) in case of plasma cholinesterase deficiency.
Hickey et al. (1987)[71]	Can J Anaesth	24-year-old, 64 kg woman with atypical plasma cholinesterase	Atracurium vs. suxamethonium	10–15 mg 2–5 mg	TOF for pollicis muscle, time for 90% first twitch blockade and recovery	Five ECT treatments	No advantage of atracurium over low-dose suxamethonium.
Dwersteg and Avery (1987)[51]	Convulsive Therapy	33 year-old white man with thermal injuries requiring ECT; weight: 47 Kg	Atracurium	0.5 mg/kg	Twitch depression measured with a force displacement transducer (Grass FT-10)	Bilateral, 13 ECT treatments	Atracurium is a safe alternative to suxamethonium in burned patients.
Dodson (1985)[76]	Br J Anaesth	1 patient with sensitivity to suxamethonium (bronchospasm)	Suxamethonium, atracurium, and mivacurium	30 mg, 2.5 mg, and 2 mg	N/A	N/A	Mivacurium provided satisfactory modification of ECT.
Sorbye (1954)[150]	Svenska Lakartidn, abstract	N/A	Suxamethonium vs. flaxedil	N/A	N/A	N/A	N/A
Thesleff et al. (1952)[151]	Am J of Psychiatry	136 patients (55 men)	Suxamethonium in mixture with barbiturate	0.2–0.4 mg/kg	Respiratory effort and time of spontaneous return after anaesthesia	512 ECT treatments	Suxamethonium is suitable for routine use in connection with ECT.

BMI, body mass index; ECT, electroconvulsive therapy; N/A, not available; NMBA, neuromuscular blocking agent; NMS, neuroleptic malignant syndrome; TOF, train-of-four; EEG, electroencephalography, MH, malignant hyperthermia.

CONCLUSION

Neuromuscular blockade has dramatically reduced the incidence of important complications such as vertebral fractures and physical injuries related to ECT. With a rapid onset of action and short duration of effect, suxamethonium remains the NMBA of choice for ECT. However, significant comorbidities may require modification of the anaesthetic regimen and avoidance of suxamethonium. Nondepolarizing NMBAs are effective when suxamethonium is contraindicated. Clinicians should use quantitative or qualitative assessment of the neuromuscular transmission and pharmacological reversal of the neuromuscular blockade when nondepolarizing NMBAs are administered. Sugammadex provides rapid and reliable reversal of neuromuscular blockade after vecuronium and rocuronium, and the combination of steroidal NMBAs and sugammadex may be an attractive alternative to suxamethonium for ECT.

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3

Optimal Doses of Succinylcholine and Rocuronium during Electroconvulsive Therapy: A prospective, randomized, crossover trial

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Accepted, Anesthesia and Analgesia

ABSTRACT

Background

Neuromuscular blockade is required to control excessive muscle contractions during electroconvulsive therapy (ECT). In a crossover, assessor-blinded, prospective randomized study, we studied the optimal effective dose of succinylcholine and rocuronium for ECT, defined as the lowest dose to provide acceptable control of muscle strength during induced convulsions.

Methods

Succinylcholine (0.8 $mg.kg^{-1}$) or rocuronium (0.4 $mg.kg^{-1}$) were randomly administered in 227 ECT sessions to 45 patients. The dose was incrementally increased or decreased by 10% based on two psychiatrists' (blinded to treatment) assessment of 'acceptable' or 'not acceptable' control of evoked muscle contractions (sufficient vs. insufficient or excessive paralysis). The neuromuscular transmission was monitored quantitatively until full recovery.

Results

The optimal effective doses of succinylcholine and rocuronium in 50% of patients (OED_{50}) were 0.85 $mg.kg^{-1}$ (95% CI: 0.77-0.94) and 0.41 $mg.kg^{-1}$ (95% CI: 0.36-0.46), and the 90^{th} percentile of the applied optimal doses (OED_{90}) 1.06 $mg.kg^{-1}$ (95% CI: 1.0-1.27) and 0.57 $mg.kg^{-1}$ (95% CI: 0.51-0.62), respectively. Nadir twitch height for acceptable muscle activity was 0% [0-4] and 4% [0-30] ($p<0.001$), and the time to recovery of the neuromuscular transmission after optimized induced seizure 9.7 ± 3.5 and 19.5 ± 5.7 min, respectively. The inter-individual variability of the OED_{50} (coefficient variation) was 1.24-fold greater for succinylcholine than rocuronium.

Conclusion

A twitch suppression of more than 90% is needed for control of motor contractions during ECT. Succinylcholine doses of 0.85-1.06 $mg.kg^{-1}$ produce acceptable muscle blockade. Rocuronium is a safe alternative if appropriately dosed (0.41-0.57 $mg.kg^{-1}$) and monitored.

INTRODUCTION

Electroconvulsive therapy (ECT) is a treatment in which generalized seizures are induced by transcutaneous electrical stimuli to the brain to treat specific psychiatric conditions such as therapy-resistant depression, catatonia and therapy-resistant schizophrenia. [1, 2] The quality and duration of the induced seizure by ECT have been associated with the efficacy of the procedure. Anesthetic drugs and neuromuscular blocking agents (NMBAs) are administered to ensure patient comfort and safety, but need also be titrated to provide optimal conditions for the induced seizure activity during the treatment, while allowing a rapid recovery upon its completion.[3] Due to its rapid onset and short duration of action, succinylcholine is considered the NMBA of choice for ECT. However, a non-depolarizing NMBA needs to be considered in some patients with metabolic, neuromuscular or neurological comorbidities, or other contraindications to succinylcholine (e.g. immobilization or pseudocholinesterase deficiency).[4] Despite the importance of NMBAs to provide favorable conditions for ECT, the optimal NMBA dose to achieve acceptable level of muscle contracture using neuromuscular blockade without excessive or untoward effects has not previously been identified in a prospective randomized fashion and using objective monitoring techniques.[5] The aim of this study is, therefore, to identify the optimal NMBA doses of two commonly used neuromuscular blocking agents (succinylcholine and rocuronium), defined as the lowest dose to provide optimized muscle strength modulation during ECT.

MATERIALS AND METHODS

This cross-over randomized controlled, assessor blinded clinical trial was conducted in the post-anesthesia care unit at Massachusetts General Hospital in Boston, MA, USA. Institutional Review Board approved the study protocol, and written informed consent was obtained from all participating patients.

Patients

Two hundred and twenty-seven ECT sessions were conducted in 45 hospitalized patients aged 24-80 years with American Society of Anesthesiologist Class I -III, admitted for a series of ECT treatments at a frequency of 3 times per week. The indication for ECT in all enrolled patients was major depressive disorder or bipolar disorder, and all patients were taking psychotropic medications including antidepressants and antipsychotics, as indicated by their psychiatric condition. Only patients within 20% of the ideal body weight were included. Exclusion criteria included an age of <18 years, patients with illness or medications known to influence neuromuscular transmission, significant renal or liver dysfunction, electrolyte abnormalities and pregnant women.

Protocol

The flow of patients through the study is depicted in figure 2. Following screening by the psychiatrist and anesthesiologist responsible for the clinical treatment of each patient, informed consent was obtained and patients were enrolled. After preoxygenation with 100% oxygen for 3 minutes through a facemask, anesthesia was induced with propofol (1.2 $mg.kg^{-1}$ intravenously over 5 sec). Continuous neuromuscular transmission monitoring was applied after stabilization and baseline calibration to establish a control twitch response prior to NMBA injection (see below). Succinylcholine (Quelicin®, Hospira Inc., Lake Forest, IL) 0.8 ($2.67 \times ED_{95}$) $mg.kg^{-1}$ or rocuronium-bromide (Zemuron®, Oganon USA Inc) 0.4 $mg.kg^{-1}$ ($1.33 \times ED_{95}$) was then administered intravenously over 5 sec via an intravenous catheter in the arm contralateral to the side of neuromuscular transmission monitoring, which was then flushed with a 10 ml bolus of normal saline. These initial doses were selected as the median of applied succinylcholine and rocuronium doses to achieve acceptable ECT induced motor activity in pilot study of 10 patients. Ventilation was assisted until recovery of normal spontaneous ventilation via a facemask and an Ambu-bag with supplemental 100% oxygen. After the peak effect of neuromuscular transmission blockade was established, an electrical stimulus at approximately 6x seizure threshold was delivered with right unilateral application of electrodes with a MECTA Model SR II apparatus (MECTA Corp., Portland, OR, USA). The treating psychiatrists, blinded to the type and dose of the NMBA (see discussion), determined the stimulus parameters for the applied ECT (level, dynamic, energy, intensity and duration of stimulus) and the subsequent duration of seizure (Table 2). The duration of seizure was monitored by EEG and recorded from EEG activity.

Systolic and diastolic blood pressures (SBP and DBP) were recorded every 3 min and the heart rate (HR), and oxygen saturation (SpO_2) were monitored and recorded continuously throughout the procedure and until full recovery. Temperature was monitored and maintained ≥ 35°C. Labetalol (10-50 mg IV) or esmolol (40-80 mg IV) was administered to treat hypertension and tachycardia, when necessary.

After termination of seizure and when appropriate, as determined by the practicing anesthesiologist, the rocuronium-induced neuromuscular blockade was reversed with neostigmine 50 $microgram.kg^{-1}$, administered with glycopyrrolate 10 $microgram.kg^{-1}$. [6] After return of normal spontaneous breathing, patients were placed in a lateral decubitus position. Neuromuscular monitoring was continued until full recovery of the neuromuscular blockade was recorded (T1 =100% or TOF ratio of > 0.9 for succinylcholine and rocuronium, respectively). [7]

Neuromuscular transmission monitoring

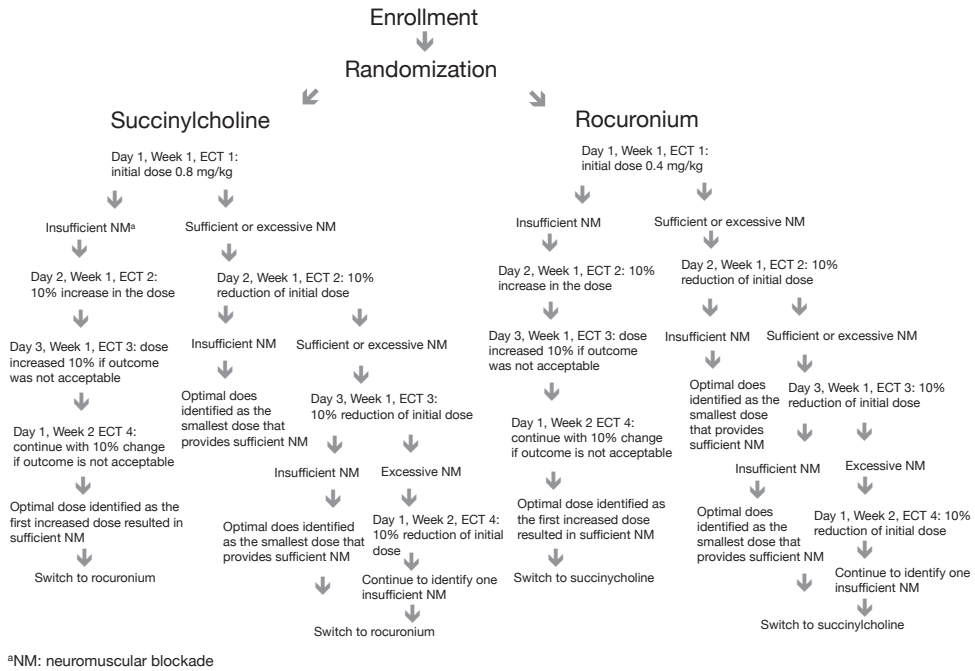
Neuromuscular transmission was monitored using acceleromyography and a TOF-Watch SX® monitor (Organon, Roseland, NJ, USA) connected to a laptop computer. Before induction of anesthesia, the subject's arm was taped in a stable and comfortable position, skin was cleansed and surface electrodes were placed (3-5 cm apart) over the ulnar nerve at the wrist. A hand adaptor (Organon International Inc., Roseland, NJ, USA) was used to fix the thumb position to minimize the potential variability in evoked muscle contraction. The TOF-watch was calibrated by using the standard calibration with default supramaximal stimulation (CAL1: 10 sec stimulation current of 50 mA), and ulnar nerve stimulation was resumed with single twitch stimulation at 0.1 Hz and continued till observation of less than 5% variation of twitch heights for 2-3 min, after which a bolus dose of the NMBA was injected.[8] The same mode of stimulation was continued until the peak effect of neuromuscular transmission blockade was established (first of three consecutive twitches with the same/increasing value or ≥ 95% depression of twitch). [8] After completion of the ECT- induced seizure, twitch stimulation was continued in patients who had received succinylcholine until a twitch height of 100% of control (baseline) with response variation less than 5% for 2 min was recorded.[8] For rocuronium-treated patients the mode of stimulation was changed to TOF-stimulation with square wave pulses of 0.2 msec duration delivered at 2 Hz every 15 sec, and continued until three consecutive responses with a TOF ratio ≥ 0.9 were recorded. All twitch height values during the recovery phase were normalized to final twitch value, and were expressed as percentages of control values. [8]

NMBA randomization and crossover

Patients were randomized to receive either succinylcholine or rocuronium at a standard initial dose, as listed above, during their first ECT. During each subsequent ECT treatment (two days apart), patients received a 10% higher (if insufficient paralysis) or lower (if sufficient or excessive paralysis) dose of the same NMBA until the *minimum effective dose* that resulted in acceptable muscle relaxation (defined as the *optimal dose*) was identified. When the optimal dose of the first NMBA was identified, each patient received the second NMBA (i.e. succinylcholine if rocuronium had been administered, and vice versa) for his or her subsequent ECT treatments, and the dose was increased or decreased in 10% increments according to the same protocol until the minimum acceptable dose for the second NMBA was established (Figure 1, study design).

Quality assessment of muscle relaxation

The quality of muscle relaxation during seizure was independently assessed using a dichotomous scale of 'acceptable' or 'not acceptable' by two psychiatrists, who were blinded to the dose and type of NMBA. A grading system was used to score the two



[a]NM: neuromuscular blockade

Figure 1. Study design

psychiatrists' evaluation. Each psychiatrist provided a single score based on defined criteria for 'acceptable' or 'not acceptable' ECT conditions (Table 1). A summed score of more than or equal to two was considered as 'acceptable' level of induced muscle relaxation. Any summed score of less than two was considered as 'not acceptable' level of induced muscle relaxation. Consequently, NMBA trials were continued until the lowest dose that provided acceptable relaxation during induced seizure was identified.

Outcome Variables

The primary clinical outcome of the study was to define the optimal effective dose (OED) of succinylcholine and rocuronium for each subject to achieve acceptable level of muscle relaxation, defined as the smallest dose of succinylcholine or rocuronium that resulted in adequate muscle relaxation and safe application of ECT in 50% of the cases (OED_{50}). We also provide the NMBA dose that resulted in adequate relaxation in 90 and 95% of the population (OED_{90} and OED_{95}) and the nonparametric bootstrap confidence intervals for the upper tail distribution of the optimal doses. The measured OED_{50}s of succinylcholine and rocuronium and the corresponding T1 suppression for acceptable motor activity during ECT are comparable to their ED_{95}s (median dose corresponding to more than 95% twitch

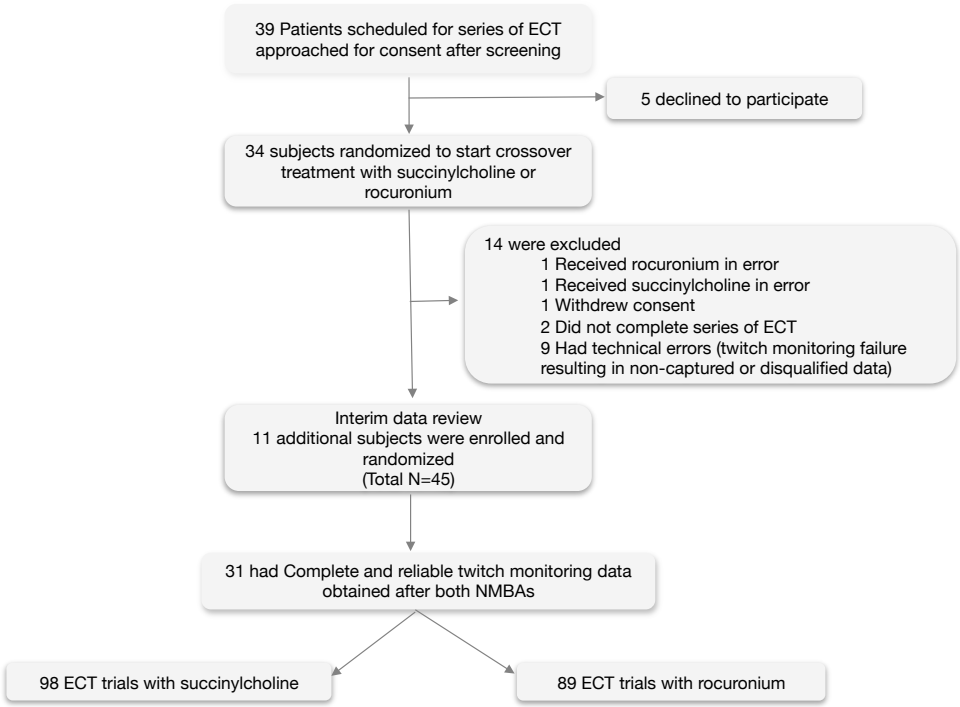


Figure 2: Schema of the study methods. After screening for eligibility criteria, we enrolled consecutive patients who scheduled for series of electroconvulsive therapy after consenting to participate in the study. Only captured data from patients who completed the series of treatments with reliable neuromuscular monitoring were used for analysis.

depression[9]), i.e. m×ED_{95} under the conditions studied (ECT).

The secondary outcome was the duration of the neuromuscular transmission blockade; defined as the time to complete recovery from neuromuscular blockade after a single bolus dose of the OED_{50}, i.e. return of the twitch height to its baseline if succinylcholine had been administered, or TOF ratio ≥ 0.9 if rocuronium was used. All patients were monitored until full recovery from neuromuscular blockade (twitch height of 100% or TOF ratio ≥ 0.9 for succinylcholine and rocuronium, respectively).

Additionally, the coefficient of variation (CV), a measure to show the relative variability of OEDs in each treatment group (succinylcholine and rocuronium), was calculated and compared, as well as the quartile coefficient of dispersion of the OEDs to make comparison of dispersion of OEDs within and between the treatment groups.

Table 1. Definitions of conditions and terms for assessing the quality of "acceptable" or "not-acceptable" muscle relaxation during ECT induced seizure. Each assessor (psychiatrist) provided a separate score. A minimum summed scores of 2 or more was considered as "acceptable" muscle relaxation.

Condition	Term	Score
Excessive relaxation during seizures	Evidence of electric seizure present from EEG monitoring or increase in heart rate, but complete absence of clonic movements or generalized tonic–clonic seizure less than 15 sec	0 (Poor)
Insufficient relaxation during seizures	Sudden/brisk muscle jerks at the stimulus delivery in limbs, trunk or neck, or subsequently during the seizure presence of tonic-clonic movements in one or more limbs (entire limb), or trunk	0 (Poor)
Adequate relaxation during seizures	Freely movable joints from loss of muscle tone, absence of a plantar withdrawal response, disappearance of deep tendon reflexes, disappearance of fasciculation**,** generalized tonic–clonic of more than 15 sec	1 (Good) or 2 (Excellent)

Statistical Analysis

Data are presented as mean ± SD or [range] unless otherwise specified. Based on the results from previous NMBA dose-repose studies, we considered a minimum samples size of 24 to be adequate for the estimation of ED50 with 80% power and with a reasonable degree of assurance. [10, 11] In addition, we conducted a power analysis to determine the sample size needed for our secondary outcome parameters; the duration of block and time to recovery. In our pilot data from10 patients, a 3-min difference in recovery endpoints (100% twitch height recovery or TOF ≥0.9 for succinylcholine and rocuronium, respectively) with a standard deviation of 5 min was observed. Assuming a normal distribution of the data, we calculated a sample size of 31 to achieve 90% power to detect a mean of paired differences of 3.0, with a known standard deviation of differences of 5.0 and with a significance level (alpha) of 0.05 using a two-sided Wilcoxon test. Accordingly, we concluded that a sample size of 31 would provide adequate power for both of our clinical outcome parameters.

All the calculations were performed using "SPSS Statistics for Windows, Version 19.0 (Armonk, NY: IBM Corp., USA, IBM Corp. 2010)", "PASS 11 (NCSS, LLC. Kaysville, Utah, USA, 2011)" and SigmaPlot 11 (Systat Software, San Jose, CA). R Package 'MBESS' was used to construct the confidence interval for the CVs of succinylcholine and rocuronium OEDs and other applied doses. [12] Normality assumption of the measured variables was

Table 2. ECT parameters as well as hemodynamic, acceleromyographic and clinical characteristics of subjects after muscle relaxation with succinylcholine or rocuronium under optimized induced seizure activity (* significant at p-value cutoff of 0.01)

Variables	Optimized Induced Neuromuscular Transmission		Mean differences (SD)	P value	Correlation	P value
	Succinylcholine N=31	Rocuronium N=31				
ECT parameters (range)						
Pulse width (miliampere)	0-2	0-2				
Energy (joule)	38-110	32-116	+2.1	0.631	-0.1	0.54
Duration (sec)	3-8	2-8	-0.14 (1.9)	0.642	-0.02	0.32
Mode (up/down)	Up	Up				
Frequency (hertz)	40-90	40-90				
Duration of seizure (sec)						
Mean (SD)	27 (14)	31 (11)	-4 (18)	0.003*	-0.03	0.85
Range	10-90	10-51				
Nadir preprocedural SpO_2						
Mean (SD)	92 (4) %	94 (3) %	-2 (4)	0.011	0.16	0.33
Range	79-99 %	85-100 %				
Propofol dose (mg)						
Mean (SD)	100 (28)	107 (29)	-7 (33)	0.463	0.16	0.334
Pre-ECT heart rate (per min)						
Mean (SD)	80 (18)	81 (16)	-1 (17)	0.818	0.46	0.81
Range	42-119	53-125				
Pre-ECT systotlic blood pressure (mmHg)						
Mean (SD)	130 (17)	128 (15)	+2 (25)	0.655	-1.35	0.412
Range	101-175	94-159				
Pre-ECT diastolic blood pressure (mmHg)						
Mean (SD)	72.3 (12)	71.8 (10)	0.5 (15)	0.845	0.063	0.7
Range	54-102	53-94				
Post-ECT heart rate (per min)						
Mean (SD)	76.1 (18)	77.6 (17)	-1.5 (20)	0.647	0.37	0.65
Range	37-118	46-115				
Post-ECT systolic blood pressure (mmHg)						
Mean (SD)	147.6 (33)	152.6 (42)	-5 (53)	0.564	-0.027	0.87
Range	85-208	65-215				
Post-ECT diastolic blood pressure (mmHg)						
Mean (SD)	81 (19)	86 (23)	-5 (29)	0.337	0.081	0.62
Range	51-132	33-131				
Nadir T1						
Median, Mode	0, 0	4, 0	-4 (7)	<0.001*	-0.15	0.36
Range	0-10	0-30				
Time to 100% T1 recovery (min)						
Mean (SD)	9.7 (3.5)	13.2 (3.3)	-3.5 (5)	<0.001*	-0.19	0.25
Range	3-20	7-24				
Time to TOF > 0.9 (min)						
Mean (SD)	n/a	19.5 (5.7)	-	-	-	-
Range		8-30				
Time to first spontaneous breathing (min)						
Mean	4.4 (1.2)	6.6 (1.6)	-2 (1.5)	<0.001*	0.18	0.27
Range	2-9	4-10				
Time to Eye Opening (min)						
Mean (SD)	10 (3.3)	13 (3.4)	-3 (3.3)	<0.001*	0.134	0.4
Range	2-18	6-22				

assessed using the Lilliefors test (all $p > 0.12$ and N=31). Welch's t-test was conducted to compare the measured variables (e.g. recovery time, duration of seizure, and hemodynamic

variables etc.) obtained under succinylcholine and recouronium conditions ($p > 0.01$). [13, 14] Cohen's Kappa for inter-rater reliability was used to assess inter-rater reliability between the two assessors of motor seizure activity during ECT. The optimal effective dose of NMBA (OED) was defined as the lowest dose that provided completion of ECT under acceptable conditions. The "optimal" doses obtained from the study patients (31 optimal doses for either of treatment groups, succinylcholine or rocuronium) were resampled 10000 times using the nonparametric bootstrap method.[15] The 25th, 50th (median), 75th, 90th and 95th percentiles of these samples and the corresponding 95% and 99% confidence intervals were then calculated.

Covariates included were age, ASA Physical Status, anesthetic dose, and the ECT parameters. A p-value < 0.05 (unless otherwise specified) was considered statistically significant and reported for a two tailed test.

RESULTS

Two hundred and twenty-seven ECT treatments in 45 enrolled subjects were recorded. Thirty-one subjects completed their series of treatment, generating a total of 187 qualified ECTs for data analysis (Figure 1). Four to 8 observations were recorded for each patient with both NMBAs. The mean age and body weight of the subjects were 50 ± 8 years [24-80, F/M: 15/16] and 80 ± 20 kg [49-109], respectively. Median of ASA physical status was II. There were no significant differences between the two groups (treated patients with optimal doses of succinylcholine or rocuronium) in baseline values of SpO_2, HR, SBP and DBP. The dose of propofol used to induce anesthesia was not different in the succinylcholine and rocuronium treatment groups (100 ± 28 mg vs. 105 ± 29 mg, $p > 0.05$) No significant difference was observed between the groups in the dose of any medications administered during ECT (e.g. esmolol and labetalol).

Primary Clinical Outcome: Optimal Effective Dose of NMBA dose and onset time

OED_{50} of succinylcholine and rocuronium were 0.85 mg.kg^{-1} (95% CI: 0.77-0.94) and 0.41 mg.kg^{-1} (95% CI: 0.36-0.46), respectively. The 90th and 95th percentile of optimal doses were amounted to 1.06 mg.kg^{-1} (95% CI: 1.0- 1.27), 1.16 mg.kg^{-1} (95% CI: 0.8-1.5) for succinylcholine and 0.57 mg.kg^{-1} (95% CI: 0.51-0.62), 0.59 mg.kg^{-1} (95% CI: 0.56-0.63) for rocuronium, respectively. The range of applied optimal doses for succinylcholine and rocuronium were [0.46-1.22] mg.kg^{-1} and [0.26-0.59] mg.kg^{-1}, respectively. Table 3 demonstrates 99% CI of the OED percentiles.

Table 3. 95% and 99% nonparametric bootstrap confidence intervals (CI) of the percentiles of optimal effective doses (OED) for succinylcholine and rocuronium. The intervals calculated using the adjusted bootstrap percentile (BCa) method.

Succinylcholine	Dose (mg/kg)	95% CI	99% CI
OED25	0.704225	(0.6077-0.7392)	(0.5979-0.7834)
OED50	0.846446	(0.7664-0.9381)	(0.7163- 0.9467)
OED75	1.019541	(0.870-1.087)	(0.859-1.103)
OED90	1.062941	(1.021-1.266)	(1.020-1.555)
OED95	1.163164	(1.085-1.555)	(1.064-1.555)
OED99	1.425879	(1.158-1.555)	(1.135-1.555)
Rocuronium			
OED25	0.365957	(0.3169-0.3932)	(0.3060-0.3952)
OED50	0.412794	(0.3577-0.4568)	(0.3471-0.4669)
OED75	0.506449	(0.4356-0.5463)	(0.4264-0.5512)
OED90	0.567167	(0.5071-0.6117)	(0.5060-0.6117)
OED95	0.587320	(0.5563-0.6294)	(0.5187, 0.6294)
OED99	0.5996132	(0.5669-0.6294)	(0.5571-0.6294)

The CV for the optimal dose of succinylcholine was 1.24-fold greater than that of rocuronium (25.7% [CI: 21-29] vs. 20.86% [CI: 20-27]). These values were not different compared to the CV of other applied doses for each NMBA (25% [CI: 22-30] and 21% [CI: 18-25] for succinylcholine and rocuronium, respectively). The quartile coefficient of dispersion succinylcholine OEDs was 1.11 that of rocuronium OEDs (0.185 vs. 0.167).

Acceptable ECT induced seizure contracture was achieved after 1.4 ± 0.5 min and 3.7 ± 1 min in the succinylcholine and rocuronium groups, respectively (p<0.001). Nadir twitch suppression to achieve an acceptable controlled seizure quality (muscle activity) was 0 ± 2% [0-10, frequency of 0: 92.5%] for succinylcholine and 4 ± 6% [0-30, frequency of 0: 40%] for rocuronium. A twitch suppression of 0-10% resulted in 100% acceptable muscle relaxation after succinylcholine (97.5%: 0-4%, 2.5%: 5-10%). When rocuronium was used, a T1 twitch value of 0-10% of baseline resulted in acceptable level of muscle relaxation in 95% of cases (60% of these patients had a T1 value of 0-4% baseline, and 35% had T1 of 5-10% baseline).

Secondary Clinical Outcome: Time to recovery from neuromuscular blockade

The time to 90% twitch recovery after succinylcholine was 9.37 ± 3.2 min, while 100 % twitch recovery was obtained after 9.7 ± 3.5 (3-20) min (Figure 3). The time to TOF recovery >0.9 was 19.5 ± 5.7 min after rocuronium (Table 2).

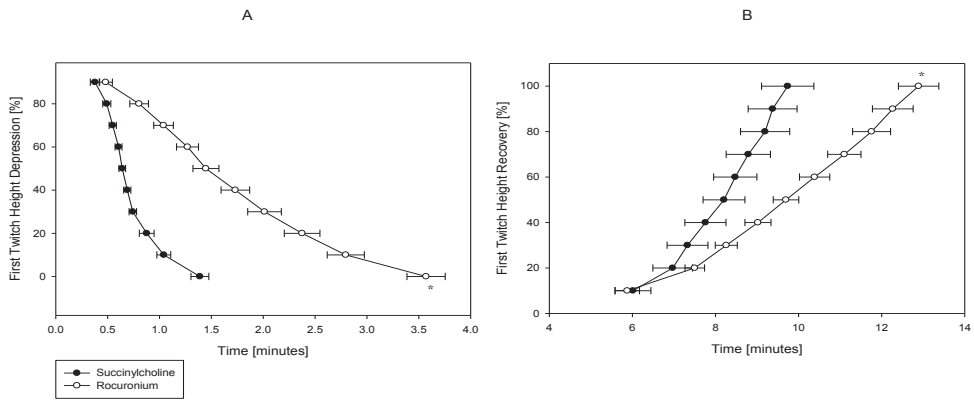


Figure 3. Time course of single twitch height (percent baseline) after injection of succinylcholine or rocuronium (Means ± SE) in optimized ECT-induced seizure quality. * P value<0.05 A. Onset of action and suppression of twitch height B. Recovery of twitch height

ECT Parameters, Hemodynamic Variables and Ancillary Data

No clinically significant differences were identified in the recorded EEG parameters or seizure quality when adequate neuromuscular blockade was obtained with rocuronium instead of succinylcholine. ECT parameters including pulse width, energy, frequency and duration were similar in both treatment groups (Table 2). No differences in HR, SBP and DBP data were observed between or within the succinylcholine and rocuronium groups. Nadir SpO_2, defined as the lowest recorded periprocedural oxygen saturation, were 94 ± 3% [85-100] and 92 ± 4% [79-99] for rocuronium and succinylcholine, respectively (p> 0.05).

The inter-rater reliability for the raters was found to be Kappa = 0.862 (p <0.001), 95% CI (0.801- 0.923). Duration of motor seizure activity following succinylcholine and rocuronium amounted to 27 ± 14 and 31 ± 11 sec, respectively (p<0.001, Table 2).

DISCUSSION

The findings reported herein indicate that near-complete twitch suppression is required for optimal neuromuscular blockade during ECT. The time to achieve acceptable neuromuscular blockade was increased by approximately 2.3 min when rocuronium was used, resulting in a total of approximately 12 min increased procedure time.

Optimal Dose of Succinylcholine and Time to Onset of Maximal Effect

Although a single best dose of succinylcholine for ECT has yet not been identified in the literature, doses between 0.5–1 mg.kg^{-1} are often used based on anecdotal reports and previous experience of anesthesia providers. [5, 16-18] Consistent with the report from Murali and his colleagues,[19] our data suggest that succinylcholine doses close to 1 mg.kg^{-1} may provide acceptable ECT conditions and also highlight the importance to avoid early application of ECT after the administration of succinylcholine (<1.4 min, time to onset of acceptable relaxation), even in the absence of a twitch response to nerve stimulation. This observation is also consistent with previous finding by Beale and colleagues[20] that the muscle response to ulnar nerve stimulation can be extinguished long before cessation of muscle fasciculation, and suggests that the time to onset of adequate relaxation for ECT is longer than the traditional 60 sec that is used for rapid sequence intubation (1 mg.kg^{-1}of succinylcholine, 3.5 × ED_{95}). [21-23] This difference in time to obtain acceptable ECT conditions as compared to that for endotracheal intubation may be attributed to a difference in sensitivity to succinylcholine in different muscle groups (e.g. oropharynx versus extremities), but can also indicate that a deeper neuromuscular blockade is needed for acceptable ECT conditions as compared to endotracheal intubation. Kopman et al.[24] showed that the speed of onset of succinylcholine might be dependent on rapid plasma clearance such that in patients with normal plasma cholinesterase activity, following an ED_{95} dose of succinylcholine time to peak effect (95% twitch depression) occurs in less than 2 min (109 sec ± 15).

The 90th percentile of the optimal effective dose of 1.06 mg.kg^{-1} (≈3.5 × ED_{95}) succinylcholine in our study and an induced twitch height suppression of 0-4% for acceptable motor seizure modification are in line with findings by Murali and his colleagues, who recommended a dose of 1.0 mg.kg^{-1} and twitch suppression to 0-5% of baseline.[19] The 95th percentile of optimal dose of succinylcholine (1.17 mg.kg^{-1}) has also been used in other clincal trials (1.2 mg.kg^{-1}). [25-28]

Duration of Paralysis and Time to Recovery after Succinylcholine

The time required for 90% twitch recovery (9.4 min) after optimal dose of succinylcholine is comparable with the reported recovery time by others after a single dose of 1 mg.kg^{-1} (9.3 min). [29, 30] Similarly, the time required for 100% twitch recovery (9.7 min) in our study is similar to that in previously published pharmacokinetic studies of this NMBA (10 minutes after applying the dose of 1.0 mg.kg^{-1}). [31, 32] Accordingly, our data suggest that the seizure-induced release of acetylcholine into the neuromuscular junction does not significantly alter the duration of succinylcholine-induced neuromuscular blockade.

Rocuronium as an Alternative to Succinylcholine during ECT

Rocuronium is increasingly employed as an alternative to succinylcholine for neuromuscular blockade during ECT, primarily in the elderly and patients with cardiovascular and neurological comorbidities. Immobilized patients and elderly or those who have suffered a stroke are particularly susceptible to succinylcholine-induced hyperkalemia due to depolarization of upregulated nicotinic (neuronal) alpha-7 acetylcholine receptors. [5] On the other hand, ECT is highly effective and is increasingly applied in the elderly and those with increased incidence of prolonged immobilization and higher risk of hyperkalemia. [5] Nondepolarizing NMBAs do not cause hyperkalemia and can be given to these patients and those with susceptibility to malignant hyperthermia or contraindications to succinylcholine, but are often avoided because of their relatively long duration of action, typically exceeding the ECT time. Moreover, there is a significant variability in the sensitivity and the time needed to obtain appropriate neuromuscular blockade after non-depolarizing NMBAs. This might explain why higher doses are often chosen to reliably obtain neuromuscular blockade for ECT, with the consequence of potentially inducing a prolonged paralysis and recovery.

Currently, rocuronium is given as a single bolus of 0.3 to 0.6 $mg.kg^{-1}$ prior to ECT treatment.[5] Doses beyond 0.4 $mg.kg^{-1}$, for ECT, have been used in combination with the reversal agent sugammadex, a selective relaxant-binding agent (currently not available in the USA), which has also been used to reverse profound rocuronium-induced neuromuscular blockade in adult surgical patients. [5] Its rapid effect on rocuronium-induced neuromuscular blockade yields recovery times that are comparable to that of succinylcholine during ECT. [5] Our study confirms that even in absence of this selective reversal agent, in patients with contraindications to the use of succinylcholine [3], the rocuronium-neostigmine combination can provide a safe and relatively time-effective alternative to succinylcholine.

Optimal Dose of Rocuronium and Time to Onset of Maximal Effect

The OED_{90} in our study (0.57 $mg.kg^{-1} \approx 2 \times ED_{95}$) is comparable to the dose that has previously been reported to induce > 95% block in 98% of subjects. [33, 34] The time needed to achieve acceptable conditions for ECT is also consistent with previous studies, with a twitch suppression to 10% baseline after 2.9 ± 1.0 min and 0% after 3.7 ± 1.0 min. The time from NMBA injection to acceptable ECT conditions is hence approximately 2.3 minutes longer with rocuronium as compared to succinylcholine. As the anesthetic agents affect the duration of the ECT-induced convulsions, clinicians should consider this difference in time from anesthesia induction to ECT application with rocuronium versus succinylcholine, and adjust the dose and timing of their hypnotic agents accordingly.

Duration of Paralysis and Time to Recovery after Rocuronium

Bevan and colleagues[35] reported the time to 90% recovery of the first twitch (T1 90) to be more than 10 min. Consistent with their data, our study showed that a twitch value of 90% was obtained after 12 min. However, in the former study, the TOF ratio of 0.9 was achieved 28 min after rocuronium-induced paralysis (0.45 $mg.kg^{-1}$). In our study, a TOF ratio of 0.9 was recorded after 19.5 min, which is comparable with a recovery time of 21 ± 4 min reported by Fuchs-Buder and colleagues [36] (after rocuronium 0.4 $mg.kg^{-1}$) and 19.4 ± 5.1 min by Lederer et al.[37] (rocuronium 0.4 $mg.kg^{-1}$).

ECT Quality and Seizure Duration after Rocuronium versus Succinylcholine

Using subjective tools to assess the recovery from neuromuscular blockade, Turkal et al.[38] reported that motor seizure duration was greater after 0.3 $mg.kg^{-1}$ rocuronium as compared to 1 $mg.kg^{-1}$ succinylcholine (33 and 24 sec, respectively). Similarly, Hoshi and colleagues [39] reported longer duration of seizure with rocuronium as compared to succinylcholine. Our data is consistent with these previously published studies confirming a small difference in seizure duration, which may be attributed to a decline in propofol-induced EEG suppression [40] after rocuronium associated with the 2 min delay in achieving appropriate muscle relaxation. As there is an association between clinical effectiveness of ECT and the duration of induced seizure[41], the American Psychiatric Association task force advocates seizure lengths > 20 sec for effective ECT treatment. [42] This recommendation underscores the importance of titrating the dose of the NMBA to achieve an adequate neuromuscular blockade. EEG monitoring is also recommended for induced seizure monitoring [43], particularly in patients who might need higher doses of an NMBA to achieve acceptable modified seizure. Further studies are needed to assess the therapeutic effects of the cumulative seizure time in a series of ECTs using optimal doses of these NMBAs.

Dose Variability with Succinylcholine versus Rocuronium

The observed inter-individual variability for the OEDs of rocuronium and succinylcholine is consistent with previously reported studies (coefficient variation of 25%, range: 15-27% for N>24[12]). As compared to rocuronium, succinylcholine showed relatively higher inter-individual variability (coefficient variation ratio of 1.24) and dispersion (the quartile coefficient dispersion ratio of 1.1) for the applied effective doses that resulted in acceptable neuromuscular blockade and controlled ECT induced seizure.

Inter-individual differences in the expression and activity of butyrylcholinesterase enzyme (BChE) is known to be of importance for the metabolism of succinylcholine [31, 44, 45], and may explain the observed difference in its dose variability when compared to rocuronium. [30] A relatively smaller OED variability for rocuronium might clinically have a greater significance

if achieving the optimized induced seizure activity is important to rapidly maximize the therapeutic effect of sequential ECTs, particularly if the use of succinylcholine is contraindicated. However, if the initial dose of rocuronium (0.4 mg.kg^{-1}) is insufficient and increasing doses are required, the duration of the induced neuromuscular blockade is less predictable. Longer recovery times that may even extend beyond the duration of the ECT should be considered. [29, 46]

Clinical implications

Due to the documented inter-individual variability in the $OED_{50\text{-}ECT}$ of succinylcholine, an initial dose of 0.85 mg.kg^{-1} is reasonable for the first ECT session, with dose adjustments in 0.1 mg.kg^{-1} increments or decrements, based on the quality of the observed motor seizure activity for each individual during subsequent treatments.

As an alternative and if clinically indicated, we suggest a 0.4 mg.kg^{-1} bolus of rocuronium as the initial dose of the applied NMBA. ECT should be applied after a twitch suppression of >90% is documented or, if twitch monitoring is not available, after sufficient time has been provided to ensure > 90% peak effect from the administered rocuronium (i.e. 3 min). If excessive or insufficient neuromuscular block is noticed during the induced seizure, dose adjustment with 0.05 mg.kg^{-1} decrements or increments is advisable. After the treatment, the rocuronium-induced neuromuscular blockade should be reversed in the regular fashion with neostigmine (50 microgram.kg^{-1}). Due to inter-individual variability in the time to recovery, particularly if doses in excess of 0.6 mg.kg^{-1} are administered, quantitative NMT monitoring is recommended to evaluate adequate level of relaxation and to ensure sufficient recovery of the induced neuromuscular blockade, in order to minimize the risk for adverse respiratory events. [5, 47] Clinicians should ensure that all patients stay under close observations by appropriately trained personnel, and continue to monitor the neuromuscular function until complete recovery of the neuromuscular transmission has been verified (e.g. sustained head lift or tongue depressor test). [48]

In summary, the presented data shows that a twitch suppression of > 90% is required for acceptable neuromuscular blockade during ECT. The time to achieve acceptable neuromuscular blockade is increased by approximately 2.3 min when rocuronium is used instead of succinylcholine, resulting in an average of 12 min increased procedure time. When appropriately dosed and monitored, rocuronium can be a safe alternative NMBA for electroconvulsive therapy in patients with contraindications to succinylcholine.

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SUPPLEMENTARY APPENDIX

Bootstrap method for estimation of OED_5 confidence intervals (CI) and resampling for evaluating the effect of sample size on estimated confidence limit

The data from of 31 subjects who were evaluated in our randomized crossover trial for application of rocuronium and succinylcholine in ECT were used for analysis. This approach resulted in 31 minimum effective doses of rocuronium and 31 minimum effective doses of succinylcholine resulted in acceptable induced seizures among subjects. Using "boot" package in R statistical software, 10000 bootstrap replications, bias corrected 95% and 99% confidence intervals (CIs) for the median of the optimal effective doses (OED_{50}) of rocuronium and succinylcholine were estimated. Similarly, CIs of 90 and 95 percentiles of the optimal effective doses of rocuronium and succinylcholine were calculated (OED_{90} and OED_{95}).

To confirm that 31 subjects were sufficient to obtain reasonable 95% and 99% confidence limits of optimal effective doses of succinylcholine and rocuronium, 10, 15, 20, 25 and 30 subjects were separately resampled from the optimal effective doses. The above bootstrap technique with 10000 replications was performed in each one of the new datasets and 95% and 99%confidence limits for the estimates of the OED_{50} of each dataset were obtained. The results for the effects of sample sizes are shown below:

Variable estimate	Percentile	Number of subjects				
Succinylcholine		10	15	20	25	30
OED50	5	0.6305	0.7042	0.7135	0.7163	0.7392
	95	1.0195	1.0213	0.9504	0.9467	0.9071
	0.1	0.6117	0.7146	0.6991	0.6991	0.7246
	0.99	1.0823	1.0195	1.0305	1.0414	0.9553
Rocuronium						
OED50	5	0.3329	0.3731	0.3725	0.3674	0.3877
	95	0.5463	0.5174	0.4864	0.4746	0.4568
	0.1	0.3169	0.3660	0.3572	0.3489	0.3660
	0.99	0.5488	0.5507	0.5117	0.5064	0.4669

4

Pharmacokinetics-Pharmacodynamics relationship of Succinylcholine and Rocuronium during Electroconvulsive Therapy

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To be submitted

ABSTRACT

Background

Neuromuscular blocking agents (NMBAs) are used during electroconvulsive therapy (ECT) to mitigate the induced severe muscle contractures. The objective of this study was to analyze the pharmacokinetics-pharmacodynamics (PK-PD) relationship of succinylcholine and rocuronium during ECT.

Methods

The available data on the first twitch height (T1) of 31 patients who underwent ECT as well as the corresponding intravenously applied doses of succinylcholine and rocuronium were used for the analyses in the study. The T1% (percentage change from the response to the supramaximal stimulus) derived from continuously applied TOF Watch recording to assess the minimal effective doses of succinylcholine and rocuronium during ECT. NONMEM software was used to construct, evaluate and validate the PKPD models. The PKPD of the two NMBAs was described using a two-compartment PK model and effect compartment model. The PK-PD parameter estimates required for the simulation of blood concentration were abstracted from previously reported studies in the literature.

Results

The PD model parameter estimates for succinlcholine and rocuronium during ECT were k_{e0}= 0.04 min^{-1} (SEE=0.004) and k_{e0}= 0.17 min^{-1} (SEE=0.19), respectively. The Ce50 estimations for these two NMBAs were amounted to 0.7 µg/ml (SEE=0.06) and 1.6 (SEE=0.1), respectively. The k_{e0} for neostigmine was not estimable, however the Ce50 was measured to be 0.412 (SEE=0.06).

Conclusion

The estimated PK-PD parameters for succinylcholine and rocuronium during ECT are almost comparable to previous PK-PD estimates for these two NMBA. The observed higher Ce50 for rocuronium might explain faster recovery after ECT from NMB and warrants further investigation.

INTRODUCTION

Neuromuscular blocking agents (NMBAs), known as muscle relaxants, are key medications administered to patients undergoing electroconvulsive therapy (ECT). The induced relaxation using NMBAs averts ECT patients' unwanted severe muscular responses that might result in physical injuries such as bone fractures and unpleasant experience of the procedure.[1] These drugs also modify the quality and duration of induced seizure by ECT that has been shown to be associated with the efficacy of ECT. Anesthetic drugs and neuromuscular blocking agents (NMBAs) are administered to ensure patient comfort and safety, but need also be titrated to provide optimal conditions for the induced seizure activity during the treatment, while allowing a rapid recovery upon its completion.[2]

Succinylcholine (SUX) is a bis-quaternary ammonium compound and depolarizing neuromuscular blocking agent, has been extensively used in anesthesia of ECT. In patients without plasma cholinesterase deficiency, succinylcholine has the advantage of a rapid onset and short duration of action. Therefore, this NMBA is preferred as the main NMBA for inducing muscle relaxation during ECT.[1] In spite of common use of succinylcholine, there are medical conditions that succinylcholine do not serve as a safe NMBA an alternative NMBA might be required for the safety of patients. Succinylcholine is hydrolyzed by plasma cholinesterase. [3] Genetic variants of the plasma cholinesterases, low plasma cholinesterase activity due to an acquired deficiency (e.g. liver disease, carcinoma, debilitating disease), and other factors, among which some remain unknown, may lead to an episode of prolonged apnea after succinylcholine. [3] Because of this recognized variation in the activity of plasma cholinesterases, large intersubject differences in pharmacokinetic, pharmacodynamic, and pharmacokinetic–pharmacodynamics relations are expected. [4]

Currently, nondepolarizing NMBAs such as rocuronium bromide are being used as an alternative choice for inducing muscle relaxation during ECT. Rocuronium bromide is an aminosteroid non-depolarizing neuromuscular blocking agent with a more rapid action than other currently available non-depolarizing drugs but with duration of action considerably longer than succinylcholine vecuronium. Rocuronium acts by competing for cholinergic receptors at the motor endplate. [5]

The nondepolarizing NMBAs have longer duration of action and should be used along with reversal agents (e.g. neostigmine) to accelerate recovery from neuromuscular blockade (NMB) and prevent postoperative residual NMB. The use of anticholinesterases to reverse residual neuromuscular block is efficacious only if recovery is already established. Even in these circumstances, the full effect of anticholinesterases and recovery takes considerable

time to achieve. [6, 7] Neostigmine is a parasympathomimetic which by indirect cholinomimetic mechanism inhibits acetylcholinesterase, thereby increasing the concentration of acetylcholine in the synaptic cleft.

Hypothetically, the ideal reversal agent can be given at any time after the administration of a NMBA and completion of ECT, and is efficacious irrespective of the degree of neuromuscular blockade. It has ideally a rapid onset of action and a minimal side effect profile. [6, 7] Similarly, an ideal nondepolarizing NMBA could be an agent with short duration of action and recovery time with potentially matched with a reversal agent that could be applied at any time after achieving the desired level of neuromuscular blockade. The search for the ideal nondepolarizing NMBA involves an understanding of the factors that makes succinylcholine blockade so evanescent. This entails increasing our knowledge on pharmacology of succinylcholine and other nondepolarizing NMBAs, i.e. simultaneous measurement of their plasma concentrations or a surrogate measure (pharmacokinetics) and neuromuscular blockade (pharmacodynamics). A pharmacokinetic–pharmacodynamic analysis could help in measuring the drug effect and the relation between blood concentration and the target organ under the effect of drug.

ECT produces hemodynamic changes, including increase in cardiac output (CO) during seizure activity due to sympathetic stimulation and systemic catecholamine surges. [1] Effect of cardiac output on pharmacokinetics of has been investigated. To our knowledge there is no study in literature to include the pharmacokinetic–pharmacodynamics (PK-PD) relations/ analysis of succinylcholine and an alternative such as rocuronium during ECT. The objective of this study was to provide a quantitative model to describe the kinetics and the dynamics of succinylcholine chloride and rocuronium after the different bolus doses applied for inducing muscle relaxation in patients underwent ECT. Accordingly, the aims in model development were to establish the PK–PD model for succinylcholine and rocuronium induced NMB in patients undergoing ECT. The secondary objective was to determine if the in vitro rate of degradation recorded by neuromuscular transmission monitoring (NMT) is of predictive value for the in vivo elimination rate of succinylcholine and rocuronium in ECT patients.

MATERIALS AND METHODS

This study is a secondary analysis on the crossover randomized controlled, assessor blinded clinical trial that was conducted in the post-anesthesia care unit at Massachusetts General Hospital in Boston, MA, USA to estimate the optimal doses of rocuronium and succinylcholine for ECT. The results of the main study are presented in chapter three of this dissertation.

Study population

Two hundred and twenty-seven ECT sessions were conducted in 45 hospitalized patients aged 24-80 years with American Society of Anesthesiologist Class I -III, admitted for a series of ECT treatments at a frequency of 3 times per week. The indication for ECT in all enrolled patients was major depressive disorder or bipolar disorder, and all patients were taking psychotropic medications including antidepressants and antipsychotics, as indicated by their psychiatric condition. Only patients within 20% of the ideal body weight were included. Exclusion criteria included an age of <18 years, patients with illness or medications known to influence neuromuscular transmission, significant renal or liver dysfunction, electrolyte abnormalities and pregnant women.

Protocol

The flow of patients through the study is depicted in figure 1. Following screening by the psychiatrist and anesthesiologist responsible for the clinical treatment of each patient, informed consent was obtained and patients were enrolled. After preoxygenation with 100% oxygen for 3 minutes through a facemask, anesthesia was induced with propofol (1.2 $mg.kg^{-1}$ intravenously over 5 sec). Continuous neuromuscular transmission monitoring was applied after stabilization and baseline calibration to establish a control twitch response prior to NMBA injection (see below). Succinylcholine (Quelicin®, Hospira Inc., Lake Forest, IL) 0.8 ($2.67 \times ED_{95}$) $mg.kg^{-1}$ or rocuronium-bromide (Zemuron®, Oganon USA Inc) 0.4 $mg.kg^{-1}$ ($1.33 \times ED_{95}$) was then administered intravenously over 5 sec via an intravenous catheter in the arm contralateral to the side of neuromuscular transmission monitoring, which was then flushed with a 10 ml bolus of normal saline. These initial doses were selected as the median of applied succinylcholine and rocuronium doses to achieve acceptable ECT induced motor activity in pilot study of 10 patients. Ventilation was assisted until recovery of normal spontaneous ventilation via a facemask and an Ambu-bag with supplemental 100% oxygen. After the peak effect of neuromuscular transmission blockade was established, an electrical stimulus at approximately 6x seizure threshold was delivered with right unilateral application of electrodes with a MECTA Model SR II apparatus (MECTA Corp., Portland, OR, USA). The treating psychiatrists, blinded to the type and dose of the NMBA determined the stimulus parameters for the applied ECT (level, dynamic, energy, intensity and duration of stimulus) and the subsequent duration of seizure. Systolic and diastolic blood pressures (SBP and DBP) were recorded every 3 min and the heart rate (HR), and oxygen saturation (SpO_2) were monitored and recorded continuously throughout the procedure and until full recovery. Temperature was monitored and maintained ≥ 35°C. Labetalol (10-50 mg IV) or esmolol (40-80 mg IV) was administered to treat hypertension and tachycardia, when necessary.

After termination of seizure and when appropriate, as determined by the practicing anesthesiologist, the rocuronium-induced neuromuscular blockade was reversed with neostigmine 50 microgram.kg^{-1}, administered with glycopyrrolate 10 microgram.kg^{-1}.[8] After return of normal spontaneous breathing, patients were placed in a lateral decubitus position. Neuromuscular monitoring was continued until full recovery of the neuromuscular blockade was recorded (T1 =100% or TOF ratio of >0.9 for succinylcholine and rocuronium, respectively).[9]

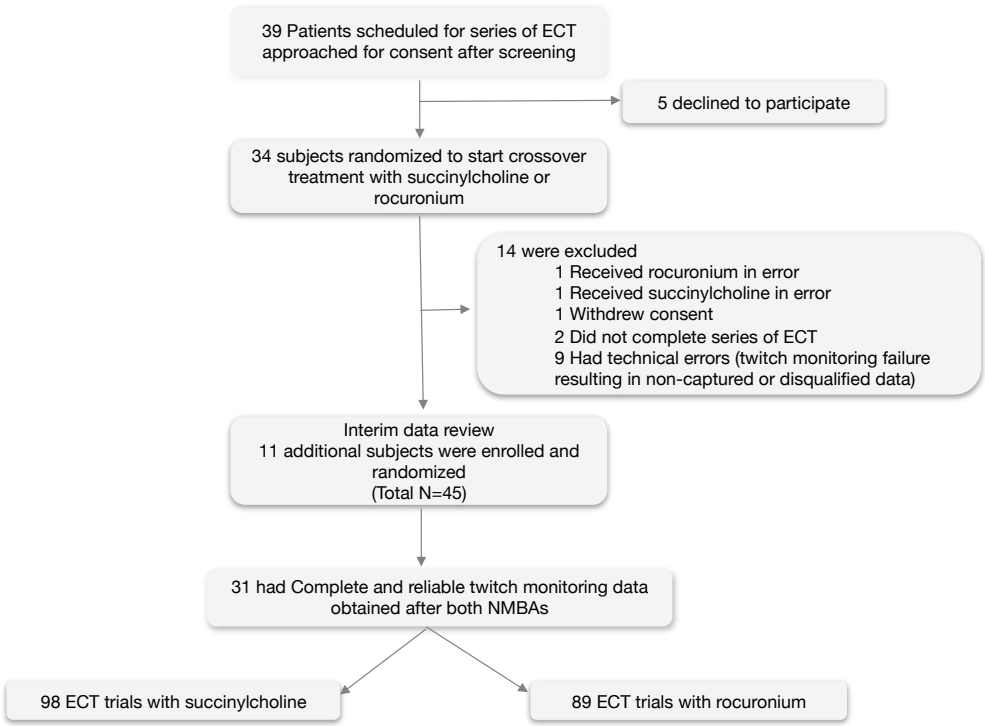

Figure 1. Patient flow through the study

Neuromuscular transmission monitoring

Neuromuscular transmission was monitored using acceleromyography and a TOF-Watch SX® monitor (Organon, Roseland, NJ, USA) connected to a laptop computer. Before induction of anesthesia, the subject's arm was taped in a stable and comfortable position, skin was cleansed and surface electrodes were placed (3-5 cm apart) over the ulnar nerve at the wrist. A hand adaptor (Organon International Inc., Roseland, NJ, USA) was used to fix the thumb position to minimize the potential variability in evoked muscle contraction. The TOF-

watch was calibrated by using the standard calibration with default supramaximal stimulation (CAL1: 10 sec stimulation current of 50 mA), and ulnar nerve stimulation was resumed with single twitch stimulation at 0.1 Hz and continued till observation of less than 5% variation of twitch heights for 2-3 min, after which a bolus dose of the NMBA was injected.[10] The same mode of stimulation was continued until the peak effect of neuromuscular transmission blockade was established (first of three consecutive twitches with the same/increasing value or ≥ 95% depression of twitch).[10] After completion of the ECT- induced seizure, twitch stimulation was continued in patients who had received succinylcholine until a twitch height of 100% of control (baseline) with response variation less than 5% for 2 min was recorded.[10] For rocuronium-treated patients the mode of stimulation was changed to TOF-stimulation with square wave pulses of 0.2 msec duration delivered at 2 Hz every 15 sec, and continued until three consecutive responses with a TOF ratio ≥ 0.9 were recorded. All twitch height values during the recovery phase were normalized to final twitch value, and were expressed as percentages of control values.[10]

NMBA randomization and crossover

Patients were randomized to receive either succinylcholine or rocuronium at a standard initial dose, as listed above, during their first ECT. During each subsequent ECT treatment (two days apart), patients received a 10% higher (if insufficient paralysis) or lower (if sufficient or excessive paralysis) dose of the same NMBA until the *minimum effective dose* that resulted in acceptable muscle relaxation (defined as the *individual optimal dose*) was identified. When the optimal dose of the first NMBA was identified, each patient received the second NMBA (i.e. succinylcholine if rocuronium had been administered, and vice versa) for his or her subsequent ECT treatments, and the dose was increased or decreased in 10% increments according to the same protocol until the minimum acceptable dose for the second NMBA was established.

Quality assessment of muscle relaxation

The quality of muscle relaxation during seizure was independently assessed using a dichotomous scale of 'acceptable' or 'not acceptable' by two psychiatrists, who were blinded to the dose and type of NMBA. A grading system was used to score the two psychiatrists' evaluation. Each psychiatrist provided a single score based on defined criteria for 'acceptable' or 'not acceptable' ECT conditions (Table 1, chapter three). A summed score of more than or equal to two was considered as 'acceptable' level of induced muscle relaxation. Any summed score of less than two was considered as 'not acceptable' level of induced muscle relaxation. Consequently, NMBA trials were continued until the lowest dose that provided acceptable relaxation during induced seizure was identified.

Outcome variables for PK-PD analysis

The primary clinical outcome of the main study (chapter three) was to define the optimal effective dose (OED) of succinylcholine and rocuronium for each subject to achieve acceptable level of muscle relaxation, defined as the smallest dose of succinylcholine or rocuronium that resulted in adequate muscle relaxation and safe application of ECT in 50% of the cases (OED_{50}).

The secondary outcome of main study was the duration of the neuromuscular transmission blockade, defined as the time to complete recovery from neuromuscular blockade after a single bolus dose of the OED_{50}, i.e. return of the first twitch height to its baseline for both if succinylcholine and succinylcholine and additional measure of TOF ratio ≥ 0.9 if rocuronium was used. To evaluate the secondary outcome of the primary analysis, all patients were monitored until full recovery from neuromuscular blockade (twitch height of 100% or TOF ratio ≥ 0.9 for succinylcholine and rocuronium, respectively). Using this data and for pharmacokinetic–pharmacodynamics (PK–PD) analysis in this study, we extracted all the measured first twitched (T1s) changes during the NMBA onset of action and recovery from the induced neuromuscular blockade (NMB), corresponding to the applied doses (both optimal and suboptimal doses). Accordingly, we generated two data sets for PK-PD analysis including the T1 changes in response to all the applied succinylcholine and rocuronium doses, respectively. Additionally, the measured OED_{50}s of succinylcholine (0.85 mg/kg) and rocuronium (0.41 mg/kg) and the corresponding T1 suppression for acceptable motor activity during ECT were used to compare the onset of action and recovery times for succinylcholine, rocuronium and rocuronium plus neostigmine.

The primary objective of this study was to provide a quantitative model to describe the PK-PD relationship of succinylcholine chloride and rocuronium applied doses in patients undergoing ECT. The secondary objective was to determine if the in vitro rate of degradation (T1) is of predictive value for the in vivo elimination rate of succinylcholine and rocuronium in the patient that underwent ECT procedure. Subsequent aims in model development were to establish the PK–PD model for rocuronium-induced NMB and its reversal by neostigmine.

Statistical analysis

The data were analyzed using the statistical package NONMEM, Version 7.3.0 (Icon Development Solutions, Hanover MD, USA). Pharmacodynamic parameters were assumed to be log-normally distributed across the population. Residual error was assumed to be normally distributed, but the dependent variable was constrained to lie within the interval (0,100). The Laplacian approximation was used for the estimation method. [11] The generalized additive model (GAM) procedure was used to identify covariates. [12] The GAM procedure

is a multiple nonlinear regression analysis of the empirical Bayes estimates for each of the pharmacodynamic parameters and the available covariates. [12] To assess goodness–of–fit, the coefficient of determination (R^2, figure 2) was calculated for every occasion and was used as a measure of the goodness of fit of the regression model (figure 2A and B).

Pharmacodynamic modeling

The pharmacokinetic models were coupled to an inhibitory sigmoid E_{max} model via a blood–effect–site concentration half–life $t_{1/2}k_{e0}$ ($t_{1/2}k_{e0}$: the half time of equilibration between drug concentration in the blood and drug effect; k_{e0}: the effect compartment equilibration rate constant). For neostigmine it was assumed that it increases the effect compartment concentration at 50% blockage representing (Ce50, the effect-site concentration associated with 50% maximal drug effect that often referred as the potency factor) of rocuronium with

$$Ce50_{rocneo}(t) = Ce50_{roc}.\ (1 + (Ce_{neo}(t) / Ce50_{nreo})^{\Upsilon neo}).$$

The concentration in the effect compartment,

Ce (t) is given by $dCe(t)/dt = k_{e0}.\ (Cb(t) - Ce(t))$ where Cb (t) is the blood concentration of the NMB agent or the antagonist, and $k_{e0} = \log(2) / t_{1/2}ke0$. For neostigmine, not all parameters were identifiable; and an indirect response model to describe acetylcholinesterase was deemed to be unfeasible. Therefore it was assumed that the k_{e0} of neostigmine was identical to the k_{e0} of rocuronium, and the offset of effect of neostigmine that could not be estimated from the data was removed from the model by the following formula:

$$dCe_{neo}(t) / dt = ke0_{roc}\ .\ Cb_{neo}(t)$$

The neuromuscular blockade is then given by:

$$Effect(t) = 100 / (1 + (Ce_{nmb}(t) / Ce50)^{\Upsilon nmb})$$

Selection of Pharmacokinetic Parameter Sets

Because in this study no blood samples were taken, the blood concentrations of succinylcholine, rocuronium, and neostigmine were simulated using pharmacokinetic data from previously reported parameters in the literature.

I. Succinylcholine Study

Succinylcholine pharmacokinetic parameters were taken from Roy et al. [4]; the geometric means were taken from the first six subject in Table 3 of the reference with exclusion of the seventh subject as appeared to be an outlier: V1: 0.00930 L/kg, k10: 3.87, k12: 1.25, k21:

1.46 min^{-1}.

II. Rocuronium

The rocuronium pharmacokinetic parameter set was taken from Wierda et al. [13], Table II of this reference. Vermeyen et al.'s investigation [14] found this parameter set to be the best for rocuronium among the studies that investigated the parameters of interest in the literature.

III. Neostigmine

The neostigmine pharmacokinetic parameters in adults was used as investigated by Fisher et al. [15], Table 2 of the reference. These constants were converted to central volume and rate constants: V1: 0.0400 L/kg, k10: 0.240, k12: 0.363, k21: 0.140, k13: 0.189, k31: 0.0201 min^{-1}.

RESULTS

Two hundred and twenty-seven ECT treatments in 45 enrolled subjects were recorded. Thirty-one subjects who completed their series of treatment and complete monitoring data for first twitches were captured, were included in the PK-PD analysis. All the NMBA doses that generated acceptable and unacceptable NMB during ECT were considered for PK-PD analysis. The mean age and body weight of the subjects were 50 ± 8 years [24-80, F/M: 15/16] and 80 ± 20 kg [49-109], respectively.

The half-life of transports between the plasma and effect compartments ($t_{1/2}k_{e0}$) for succinylcholine and rocuronium were amounted to 17 min (SEE=1.6) and 3.7 min (SEE=3.7), respectively. Accordingly, the k_{e0} estimates were 0.04 min^{-1} (SEE=0.004) and 0.19 min^{-1} (SEE=0.19) for succinylcholine and rocuronium, respectively.

The estimated Ce50 for succinylcholine and rocuronium were 0.7 µg/ml (SEE=0.06) and 1.6 (SEE=0.1), respectively. For neostigmine, the constant of k_{e0} was not estimable, however, the Ce50 was estimated to be 0.412 (SEE=0.06). Table 1 (sections A and B) summarizes the parameter estimates for both succinylcholine and rocuronium/neostigmine.

Table 1. Estimated pharmacokinetic parameters for succinylcholine and rocuronium during ECT. Table 1A and 1B summarizes the measured PK-PD parameters for succinylcholine and rocuronium (reversed by neostigmine), respectively.

1A

Succinylcholine analysis

Parameter estimates				
	Estimate	SEE	W^2	SEE
[1]$T_{1/2}k_{e0}$ (min)	17.1	1.58	0.261	0.0724
[2]Ce50 (ug/ml)	0.706	0.0599	0.221	0.05
[3]ϒ (gamma)	35.1	3.78	0.351	0.104
[4]SD	8.88	0.614		

1B

Rocuronium/neostigmine analysis

Parameter estimates				
Rocuronium				
	Estimate	SEE	W^2	SEE
$T_{1/2}k_{e0}$ (min)	3.67	0.367	0.256	0.0131
Ce50 (ug/ml)	1.59	0.0977	0.0636	0.0128
ϒ	7.54	0.733	0.0875	0.0407
Neostigmine				
Ce50 (ug/ml)	0.412 2	0.06	Not estimable	
ϒ	3.49	0.594	0.444	0.171
SD	12.7	0.792		

1. Equilibration half-time
2. Median effective concentration
3. Gamma, determines the steepness of the concentration- effect relationship (the Hill factor describing sigmoidicity of the concentration-effect relation)
4. Standard deviation

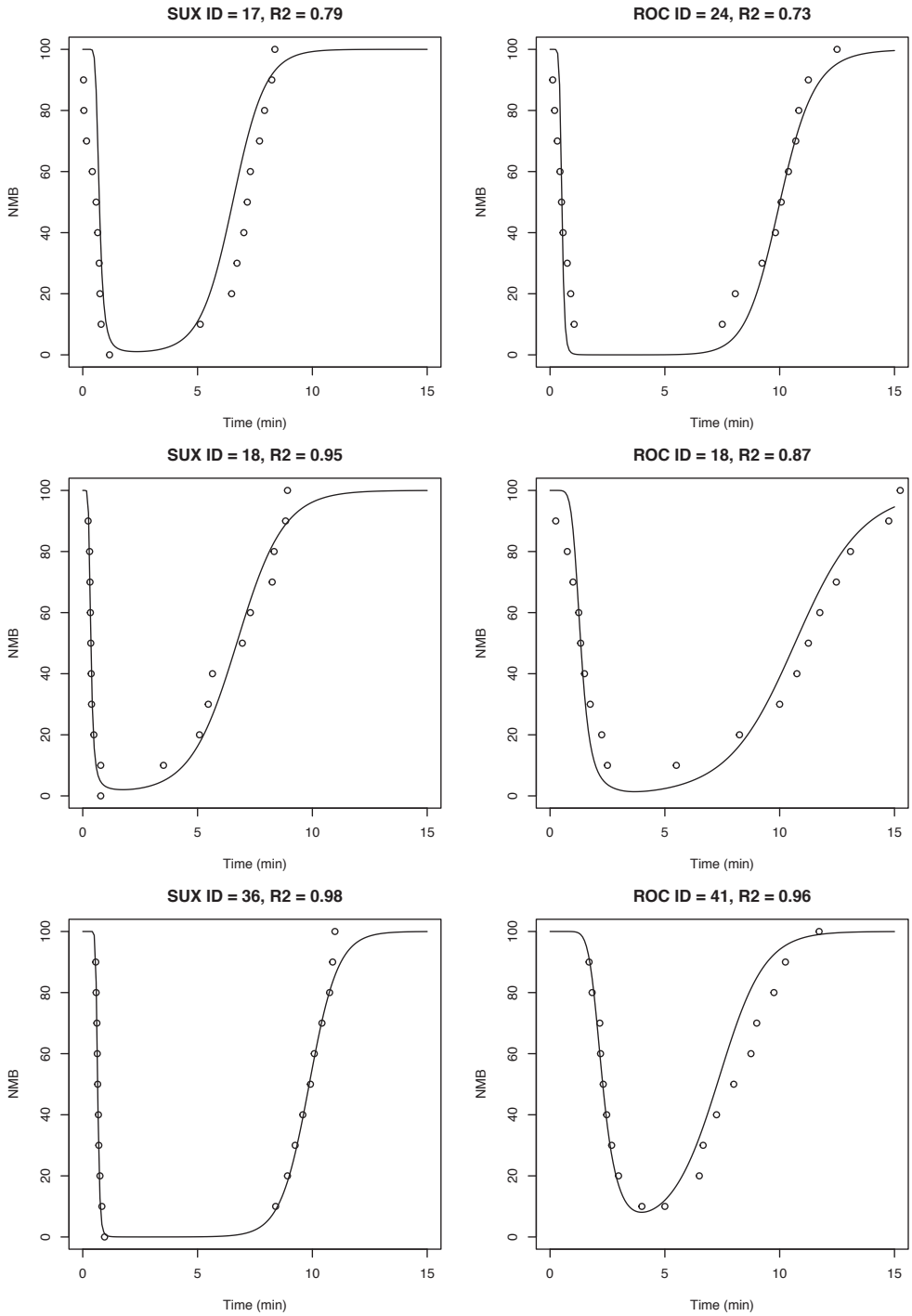

Figure 2. The plots demonstrated the examples of generated fits for individuals from data that are selected based on the range of R^2, lowest, median and highest estimated values for succinylcholine and rocuronium studies)

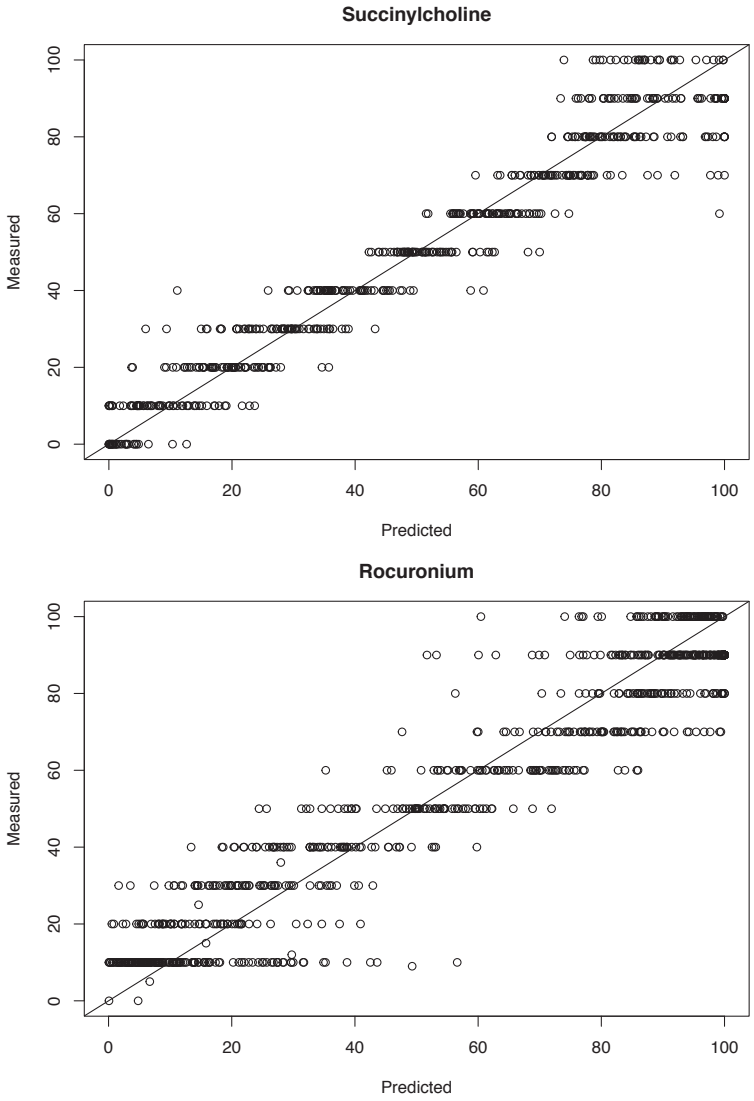

Figure 3. A and B: The graph demonstrates the goodness-of-fit plots (observed vs. predicted individual first twitch heights) for succinylcholine and rocuronium, respectively.

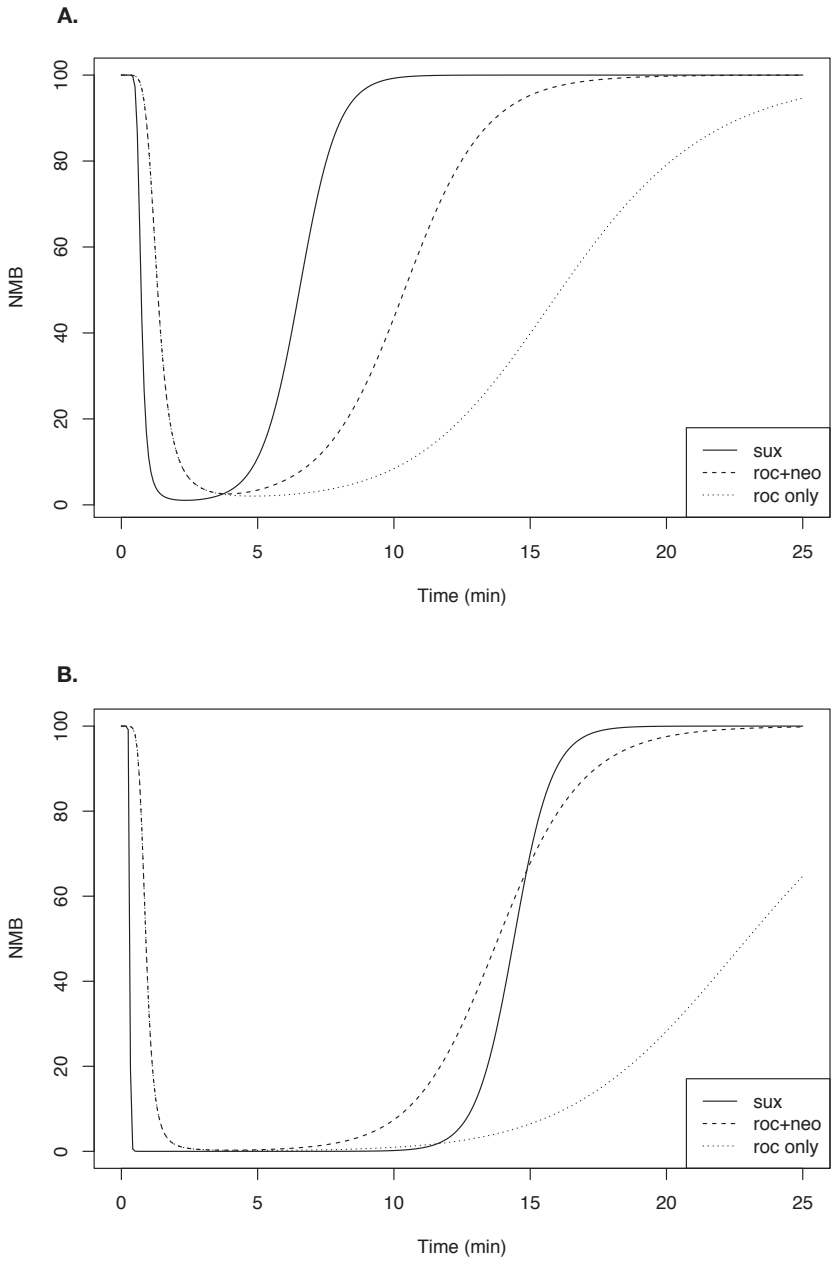

Figure 4A and B. The plots demonstrate the population simulation results for the succinylcholine and rocuronium/ neostigmine studies. In the figure A, the doses are assumed to be 0.8 mg/kg and 0.4 mg/kg for succinylcholine and rocuronium. These doses are approximately the minimal effective doses that resulted in the acceptable induced seizure during ECT in 50% of subjects (OED50). In figure B, these doses are assumed to be 1.1 mg/kg and 0.54 for succinylcholine and rocuronium, respectively. These doses are 95 percentile of minimal effective doses (OED95) resulted in acceptable induced seizure during ECT.

DISCUSSION

The half-life of transport between the plasma and effect compartment ($t_{1/2}k_{e0}$, time for effect site concentration to reach to 50% of concentration when the plasma concentration is constant) for succinylcholine at adductor pollicis in this study was almost 5 times that of rocuronium. Onset time of neuromuscular blocking drugs is determined by the time required for drug concentrations at the site of action to reach a critical level, usually that corresponding to 95% block. Onset time is longer than time to peak plasma concentrations. The faster equilibration between plasma concentrations of succinylcholine (higher $t_{1/2}k_{e0}$ -> lower k_{e0}) at adductor pollicis results in more rapid onset of blockade in adductor pollicis than rocuronium, as shown in this study.

Our succinylcholine k_{e0} estimation in this study is consistent with finding by Roy et al.[4]

The authors reported the estimate k_{e0} of 0.058 for succinylcholine. Considering their reported standard error estimate (SEE) of 0.026, our measured k_{e0} of 0.04 is a reasonable measure of k_{e0}. Furthermore our measured Ce50 of succinylcholine "the effect-site concentration associated with 50% maximal drug effect" being 0.706 ug/ml ± 0.06, is comparable to the Roy et al.'s estimate of this measurement (0.734 ± 0.211).

Plaud et al. [16] investigated the rocuronium neuromuscular blocking effect (a 5-min infusion) along with neostigmine for its reversal on twitch height in adductor pollicis and estimated the parameters of the rocuronium pharmacokinetics in relation to pharmacodymics according to Sheiner model [17], i.e., the rate constant of transport between the plasma and effect compartments (k_{e0}) and the concentration producing 50% block (Ce50). They used a two-compartmental pharmacokinetic model. These measured estimates in their study were 0.168 ± 0.06 min^{-1} and 0.823 ± 0.16 ug/ml for k_{e0} and Ce50. While the estimate of k_{e0} in our study (0.19 ± 0.19 min^{-1}) is comparable to Plaud et al.'s report, the Ce50 estimate in our study is two times of the measure (1.6 ± 0.1 ug/ml) by these authors. The effect of increasing cardiac output (CO) on the tissue clearance or distribution rate has already been shown, at least when tissue uptake is perfusion limited, as is the case with rocuronium. [18] ECT is associated with a more prominent sympathomimetic activity and an increase in CO. [19] This fact might explain higher estimated rocuronium Ce50 and subsequent the faster recovery times measured by T1 measurement in adductor pollicis that were observed in this study and ECT procedure as compared to the previous reports. [13, 20] In earlier study presented in chapter three, we also reported longer duration of induce seizure in patients who received rocuronium as NMBA. Other investigators have reported this observation, as well. [1] This observation might be another factor that potentially has affected the concentration of rocuronium in the effect

compartment. Our measured k_{e0} and $t_{1/2}k_{e0}$ for rocuronium is also consistent with the findings by Weirda et al. (0.16 and 3.85 min, respectively).[13] Cortinez et al. also measured the k_{e0} of rocuronium using both parametric and non-parametric approaches. In both methods the estimated k_{e0} was similarly 0.19 min^{-1}. [21] However, the measured Ce50 in their study was 0.92 ug/ml. Kuipers et al. [18] showed that the CO could affect some pharmacokinetics parameters and recommended using recirculatory pharmacokinetic model instead of compartmental models to include the CO effect, a matter that should be investigated in an appropriately designed ECT study.

Similar to other studies that investigated PK-PD parameters of neuromuscular blocking agents, we identified higher k_{e0} and lower EC50 for succinylcholine as compared to rocuronium. The onset time for a neuromuscular blocking agent will clinically vary according to factors such as the type of anesthesia, applied dose, type of stimulation for monitoring of neuromuscular blockade (single twitch vs. train-of-four response), and the clinical end-point used for onset time determination (peak effect or fixed degree of twitch depression) during neuromuscular monitoring. [22] Due to crossover design of our study, most of these factors were the same for both succinylcholine and rocuronium, except the applied doses that were increased or decreased to identify the minimal effective dose of each of the NMBA for inducing acceptable neuromuscular block during ECT.

The first order plasma–effect-site equilibration rate constant (k_{e0}) values might vary due circulatory factors that may, in turn alter the onset of action of a NMBA. [22] Under identical clinical settings in our study for both succinylcholine and rocuronium, the inter-individual variations in k_{e0} could explain the observed differences in the onset times and recovery times from both of the neuromuscular blockers.

The effect of drug potency in the onset of action of a neuromuscular blocking agent has been supported by several experimental studies such that there is an inverse relationship between onset times and molar potency (ED50) of NMBAs in anaesthetized patients. [23, 24] Consistent with other investigations with applied kinetic-dynamic model [25], our pharmacokinetic analysis supports the observation in onset of action for succinylcholine and rocuronium and according to these two NMBA's ED50s (figure 4A).

A higher rate constant for equilibration of the effect compartment concentration with plasma concentration (k_{e0}) and a rapid clearance after a single bolus dose of succinylcholine (recovery from block starts from distribution phase [26]) as shown in our study (figure 4A and B) has made this drug as the first choice of NMBAs for ECT. The comparison of figures 4A and 3B, derived from population analysis using NONMEM shows the increase of the applied

doses (ED95) of the succinylcholine (from 0.8 mg/kg ≈2.67 ED95 to 1.1 mg/kg ≈3.67 ED95) and rocuronium (from 0.4 mg/kg ≈ 1.33 ED95 to 0.54 mg/kg ≈ 1.8 ED95) decreases the onset of actions and increases the recovery times for both NMBAs. However, the difference in predicted recovery times decreases for the applied doses of 1.1 mg/kg vs. 0.54 mg/kg for succinylcholine and reocuronium/neostigmine, respectively. This observation suggests that in subjects in need of higher doses of succinylcholine for inducing NMB during ECT (approximately > 1 mg/kg), the recovery times might be comparable to induced NMB using rocuronium 0.5-0.6 mg/kg reversed by neostigmine 0.04-0.05 mg/kg.

There are limitations in interpretation of the results of our study to be considered. We did not measure the timely levels of NMBAs in blood after injection and during ECT. Another limitation of the study is inability to measure the neogstimine k_{eo}, in spite of the fact that we estimated neostigmine Ce50 and its effect on the reversal of rocuronium.

In this study, we identified similar pharmacokinetic-pharmacodynamic parameters (k_{e0} and Ce50) for succinylcholine during ECT as previously investigated. For rocuronium the estimated k_{e0} is consistent with others' finding, while we identified higher Ce50 at adductor pollicis that might justify the faster observed recovery from rocuronium induced NMB in this study. This observation warrants further investigation for PK-PD investigation of rocurnium during ECT in a prospective clinical trial.

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5

Pharmacogenetics in Electroconvulsive Therapy and Adjunctive Medications

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Pharmacogenomics. 2015 Jun;16(9):1015-31

ABSTRACT

Electroconvulsive therapy (ECT) has shown apparent efficacy in treatment of patients with depression and other mental illnesses who do not respond to psychotropic medications or need urgent control of their symptoms. Pharmacogenetics contributes to an individual's sensitivity and response to a variety of drugs. Clinical insights into pharmacogenetics of ECT and adjunctive medications not only improves its safety and efficacy in the indicated patients, but can also lead to the identification of novel treatments in psychiatric disorders through understanding of potential molecular and biological mechanisms involved. In this review, we explore the indications of pharmacogenetics role in safety and efficacy of ECT and present the evidence for its role in patients with psychiatric disorders undergoing ECT.

INTRODUCTION

Due to its apparent effectiveness, electroconvulsive therapy (ECT) was commonly used for depressive disorders prior to invention of antidepressants in the 1950s. At the beginning, unmodified ECT was agonizing and unsafe, leading to, among others, bone fracture or spine injury. However, the advent of anesthetics and muscle relaxants along with newer apparatus evolved the "modified ECT to achieve maximum benefits while minimizing the procedural side effects related to the applied medication (anesthesia), electrical current or the induced seizure. ECT is currently administered with individually adjusted electrical currents under surveillance of anesthesiologists who apply anesthetics and muscle relaxants in appropriate medical setting. [1]

In spite of all the technical advances that have improved the relative risk of ECT, many crucial issues remain unresolved. For example, it is difficult to determine a priori whether ECT will be associated with an "adequate" therapeutically effective seizure in each patient. [2] Genetic variations contribute to the variation of an individual's response to different class of medications or treatment procedures via multiple components. This interface between our genetic variations and response to therapeutic interventions, i.e. pharmacogenetics, determines the individual response to a specific treatment and affects both patient's safety and efficacy of response to ECT.

Historically, the role of pharmacogenetics in ECT was primarily related to the safety of ECT application and was explored by Kalow. Observation of prolonged apnea after succinylcholine administration in some individuals paved the way to the preliminary clinical insights into pharmacogenetics. In 1956, Kalow discovered that an alteration in plasma cholinesterase level caused induction of longer duration of paralysis by application of succinylcholine to ECT patients. This change resulted in extension of duration of succinylcholine action from the few minutes to over an hour in the affected individuals. [3, 4] Kalow implied the discovery of the presence of genetic effects on drug response. [5, 6]

These studies advanced further research related to pharmacogenetics such that in 1960s the process of drug acetylation was discovered and the fact that slow acetylators (poor metabolizers) are more prone to side effects related to drug metabolism. [5] Furthermore, by application of anesthetics during procedural treatments including ECT, the awareness of developing side effects such as acute porphyric event due to thiopentone as well as the observed association of the malignant hyperthermia with succinylcholine, drew the attentions in the how genetics might influence in the applied pharmacology. [7]

ECT is the most effective acute treatment for mood disorders, especially treatment-resistant Major Depressive Disorder (MDD), and has proven efficacy in other non-depressed psychiatric disorders such as schizophrenia. [8-11] Several studies have explored the impact of genetics in the neurobiological mechanisms involved in ECT. These studies have also aimed to improve the efficacy of ECT by predicting the genotype-phenotype distinction of patients undergoing ECT. [2, 12, 13] To our knowledge, no comprehensive literature review has been published on this ground. Hence, in this review, we will provide an evidence-based approach to the role of pharmacogenetics on safety (drugs used during ECT) and efficacy of ECT (potential genes and neurobiological mechanisms), and present evidence of its importance in patients with psychiatric disorders who undergo ECT (figure 1).

METHOD

Using a structured approach to identify the source of materials for the review, a systematic search was conducted for relevant peer-reviewed articles in PubMed and the Google Scholar search engine, using the keywords 'ECT anesthesia genetics', 'ECT safety genetics', 'ECT efficacy genetics', 'ECT and genetics', 'treatment resistant psychotic disorders ECT genetics', 'depressive disorders ECT genetics', 'psychotic disorders ECT genetics', 'ECT neurotransmitter genes', 'genetics and ECT response' and 'adjunctive therapy in ECT and genetics'. References of the relevant articles or editorials were also considered for potential bibliographic related references to avoid any missing publication. All searches were limited to research published in English. Due to paucity of articles on this subject, there was no restriction on time of publication. The identified papers were predominantly related to depression disorders. For the efficacy of ECT and main focus of this review, we included all preclinical and human studies that might explain a direct role of a gene in the efficacy of ECT or suggest a genetic effect through neurobiological mechanisms. Accordingly, 34 publications were identified in investigating the pharmacogenetics in efficacy of ECT; only 19 articles showed direct investigation on role of pharmacogentics in ECT. The ECT associated gene signatures were analyzed using MetaCore™ platform for investigation of their potential interactions and common biological network pathways in human brain.

PHARMACOGENETICS AND SAFETY OF ECT

I. Anesthesia adverse events

Abnormalities in butyrylcholinesterase

ECT is a short procedure and demands anesthetics with rapid onset and short duration of action. These qualities have made succinylcholine as the neuromuscular blocking agent (NMBA) of choice for ECT [1]. The enzyme butyrylcholinesterase (BCHE) hydrolyzes ester bonds in succinylcholine. The enzyme is composed of 4 identical subunits of 574 amino acids, each containing an active catalytic site. The *BCHE1* gene is located on four exons of chromosome 3q26.1–3q26.2 (online Mendelian inheritance in Man; OMIM 177400). The gene encodes a 602 amino acid protein including a 28 amino acid leader peptide. Genetic variation in the *BCHE1* gene leads to variant enzyme forms, which affect the substrate behavior, resulting in reduced or absence of the enzyme BCHE activity. BCHE deficiency results in a prolonged effect of the ultra-short acting depolarizing muscle relaxant succinylcholine due to markedly decrease in plasma cholinesterase activity [14]. The variants of *BCHE* included wild type (U), atypical (A, dibucaine resistant), fluoride resistant (F), silent (S) and Kalow (K). Besides the normal variant (U), A and K variants are more frequent (A20G and G1615A) [15]. It is noted that the patients with homozygosis or carriers with compound heterozygosity remain asymptomatic in the absence of exposure exogenous choline ester-compound such as succinylcholine.

In Australian population, out of 65 patients referred for prolonged post-succinlycholine apnea, 85% of the subjects showed one of mutated variants of *BCHE* gene including dibucaine (Dib; D70G), Sil-1 (G115FS), Flu-1 (T243M), Flu-2 (G390V), and K-variant (A539T), with 74% being dibucaine homozygote or heterozygote, 6% rare genotypes, 3% heterozygous fluoride allele, and 13% undetermined [16]. The Danish Cholinesterase Research Unit (DCRU), in a 20-year longitudinal study, found abnormal response to succinylcholine in 61.1% of the 1,247 patients who were visited in the center. Of these 1,247 patients, 28.5% had normal genotype and 46.5% were genotypically aberrant. While the recovery time of neuromuscular function in patients with one aberrant allele was 15-30 min following a single dose of succinylcholine 1.0-1.5 mg kg^{-1}, it took 35-45 min for patients with heterozygousity of abnormal allele in two genes to recover. Homozygousity in abnormal allele in atypical gene lengthened the recovery time to 90-180 min. Patients with genotypes of *AK* and *AH* experienced slightly (20 min) or markedly longer duration of action (90 min) of succinylcholine, respectively. [17] Accordingly, there are several case reports of succinylcholine induced prolonged apnea in patients receiving ECT. [1, 18-20] In a longitudinal study, Mollerup et al. determined the *BCHE* activity and the *BCHE* genotype of 13 patients who were visited in the DCRU after ECT. [21] The authors measured and compared the duration of apnea with normal subjects and found *BCHE* gene

mutations, the K-variant being the most frequent. The duration of succinylcholine action and consequently duration of apnea were prolonged (5-15 min) in 11 patients compared with controls (3-5.3 min). Consequently, they recommended neuromuscular monitoring during the first ECT.

Malignant hyperthermia

Malignant hyperthermia (MH) is a hypermetabolic response to succinylcholine and potent volatile anesthetic gases such as halothane, isoflurane, sevoflurane and desflurane. Succinylcholine, the main applied muscle relaxant in ECT, is a far more powerful trigger of MH than the volatile agents. [22-24] Experimental studies indicate that the mechanism underlying MH is an uncontrolled release of intracellular calcium from skeletal muscle sarcoplasmic reticulum (SR). MH is inherited primarily in an autosomal dominant fashion in humans, which might result in the MH prevalence of up to 1: 3000 due to the causal genetic mutation. A more complex inheritance pattern might also be observed in the affected individuals. [25]

Approximately 50% of MH related genetic variants have been found in the *RYR1* gene on chromosome 19, a calcium channel located in the sarcoplasmic reticulum. Most cases (70%) carry one of 30 *RYR1* mutations. Linkage studies have implicated five other regions, with variants identified in calcium channels *CACNA2D1* and *CACNA1S*. While these regions account for genetic variants in less than 2% of cases, the causal genetic variant in approximately 30% of patients remains unknown. [26, 27] Genetic tests may offer a non-invasive diagnostic method with lower morbidity than in vitro muscle contracture tests as the current functional gold standard for MH diagnosis; however, genetic testing is unreliable because the spectrum of contributing loci and alleles is not yet fully understood.

The reported incidence of MH during ECT has been less than other procedures requiring general anesthesia. It seems more likely that other factors may be responsible for this observation. Gornert indicated that MH is triggered in proportion to the total dose of triggering agents. [28] Thus, even if MH is triggered by succinylcholine during ECT, the absence of continued administration of succinylcholine may abort its more fulminant expression. Indeed, the anesthetics used in ECT are almost always ultra-short or short acting barbiturates such as methohexital or propofol. Absence of the use of volatile anesthetics in ECT also may explain the lack of induction of MH. As was previously stated potent volatile anesthetics that are commonly employed in general anesthesia are also strongly linked to precipitation of MH. [29]

Neuroleptic malignant syndrome

NMS is a serious and potentially fatal side effect of antipsychotics, consisting of fever, muscle rigidity, delirium and autonomic dysfunction. Underlying mechanism of this side effect is still unknown and debated. So far some risk factors have been identified, with clinical observations and recent pharmacogenetic research suggesting, though with inconsistent findings, correlation between genetic mechanisms and predisposition to NMS. [30] Polymorphisms of *CYP2D6* enzyme through which most psychotropic drugs are metabolized and TaqIA DRD2, a target for antipsychotic drugs, has been reported to act as the link between pharmacogenetic factors and the potential development of NMS. [30] In spite of these genetic links, ECT has been reported to be useful for refractory NMS or improving NMS symptoms. [31, 32] Further investigation in an appropriately designed study is warranted to investigate the treatment role of ECT in NMS and identify the subset of patients with NMS who might benefit from this procedure.

II. Potential neurobiological mechanisms in cognitive side effects of ECT

There are some animal and human preliminary evidences on the role of neurotransmitters/ biological alterations with the adverse cognitive effect of ECT. [33, 34] The investigated systematic alterations include cholinergic, endogenous opioid, glucocorticoid and glutaminergic systems, which were mostly conducted in animal models. [34-37] Among these, the effects of glutaminergic and glucocorticoid compounds have been investigated in human studies. In an ECT trial of 10 subjects, using ketamine as anesthetics resulted in less impairment of short-term memory than applying etomidate [37]. The result is suggestive that the ECT-induced cognitive disruption might be mediated by glutamate at N-methyl-d-aspartate receptors. Neylan et al. [38], in a two-week ECT-trial of 16 subjects, showed that elevated basal level cortisol was associated with greater degree of ECT-induced cognitive impairment.

Palmio et al., in two separate studies, investigated the acute effect of ECT on the perturbations in the amino acid transmitters and the brain biomarkers in blood with potential role in neuronal activity and neuronal injury. In TRD-MDD patients who underwent a single ECT session, they showed significant changes in the serum levels of glutamate, aspartate, gamma-aminobutyric acid (GABA), S-100b protein (S-100b), tryptophan, and some other amino acids in 24 hours. [39, 40] However, it is important that future studies are designed to better distinguish changes in the levels of these biomarkers related to both ECT side effects on brain and therapeutic response.

Pharmacogenetics and the efficacy of ECT

The effect of adjunctive psychotropic drugs on ECT outcome

The current remission rates after ECT appear to have declined. [8, 41] In a meta-analysis to investigate the effect of previous pharmacotherapy failure on the efficacy of ECT, the overall remission rate was reported to be 48.0% (281 of 585) and 64.9% (242 of 373) for patients with and without previous pharmacotherapy failure, respectively. Additionally, patients who received previous pharmacotherapy but failed to respond to the treatment, showed reduced efficacy of ECT. [42] ECT has shown higher efficacy in conjunction with antidepressants and antipsychotics. [43] Accordingly, the understanding of pharmacogenetics of the adjunctive drug therapy and more comprehensively pharmacogenomics of such treatments has the potential to improve therapeutic outcomes of ECT and individualized drug therapy, while avoiding toxic effects and treatment failure. Genetic predictors of antipsychotics have been widely studied [44], but fewer evidences are available how these factors might influence their role in the outcome ECT.

Some studies provide evidence that the application of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine (0.5 mg/kg) could provide rapid and longer antidepressant effects after ECT. [45-50] These studies have suggested the involvement of synaptic plasticity and neurotrophic signaling in the mechanism of action of ketamine. The observation of mammalian target of rapamycin (mTOR) and *B*rain-*D*erived *N*eurotrophic *F*actor (BDNF) pathway activation by NMDA receptor antagonism has proposed the observed link for the antidepressant action of ketamine through the interaction between plasticity-related signally pathway. [51]

Using ketamine (0.5 mg/kg) been promising in depressive patients prior to ECT. [52, 53] Some evidences that ketamine might reduce the effect of ECT on memory has drawn more attentions to application of ketamine for ECT. [37] The optimal adjunctive dose range of ketamine, its safety and effective duration of action should be further investigated.

The association between carrier status for the long allele of serotonin transporter gene with a better response to serotonin selective reuptake inhibitors (SSRIs) has been of interest. Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 (*SLC6A4*) encodes the serotonin transporter and is located on location 17q11.1–q12. Rasmussen et al. retrospectively studied whether the polymorphism of the serotonin transporter gene (*5-HTT*) was associated with differential treatment response in 83 ECT patients treated for depressive disorder. [12] No significant association was found between serotonin transporter gene allelic status with several characteristics of ECT treatment, such as seizure length or threshold, number of treatments in a series, and depression scale ratings.

Potential pharmacogenomics (neurobiological mechanisms) in the efficacy of ECT

I. Brain Alterations in Acute and chronic ECT response

As was previously stated, for many non-responsive patients to psychotropic drugs, ECT is an efficient rapid intervention. However, the neurobiological mechanisms for the efficacy of ECT remain unknown.

While some of the therapeutic response to ECT is shortly observed after treatment, similar to psychotropic drugs, efficacy of ECT increases by repeating treatment. This fact has made neurotransmitters and metabolic enzymes of greater interest for investigation of ECT response. ECT affects wide range of brain areas, [54, 55] which the potential therapeutic effects on these regions may be through structural, and/or biochemical changes.

Several neurotransmitters have been investigated involvement in association with psychotic disorders. Yatham et al. [56] suggested the role of serotonin (5-hydroxytryptamine, 5-HT) dysfunction. Using positron emission tomography (PET) study in patients with bipolar disorders, they showed antidepressants down regulate 5-HT_2 receptors in several cortical regions. In a follow-up study in patients who treated with ECT due to refractory response to antidepressants, they showed similar effect by ECT in down-regulation of brain 5-HT_2 receptors in the limbic and prefrontal cortical brain areas. [57] Similarly in another study by Lanzenberger et al., PET scan showed substantial reduction of 5-HT1A receptor-binding potential (BPND) almost across the entire cortex after one ECT, particularly in amygdala and anterior cingulate cortex. [58] However in another study, after several ECT, BPND did not show consistent result with the former study. [59]

Dopamine neurotransmitter has also been of interest in understanding the refractoriness of response to treatment in depressive disorder. Saijo et al. scanned seven MDD patients' brain after 6-7 ECTs using PET to examine the effect treatment on Dopamine D_2 receptors. They found significant increase in D_2 receptors of anterior cingulate of patients who received ECT. [60] Although these studies shows regulatory role of serotonergic and dopaminergic pathways in biological mechanisms involved in response to ECT, it is yet to be discovered how ECT cause this alterations.

A few studies on depressive disorders have explored the hypothesis of altered connectivity within the white matter (WM) microstructures between the frontal and limbic areas, [61-63] such that WM abnormalities relate to depression severity and TRD. [64-67] Accordingly, Lyden et al. demonstrated ECT effect on structural plasticity within dorsal fronto-limbic pathways and plasticity of WM relation to therapeutic response in depression. [67] It is unknown if there is any genetic predisposition to these structural alteration, and future investigation is hence

warranted.

II. Potential genes involved in ECT response and the related biological pathways

In 1998, Fochtmann et al. showed that both hippocampal A1-receptor, and cortical and striatal *NMDA*-receptor bindings are associated with the quality of seizure (i.e. duration). [2]Their study suggested that induced ECT-neurobiological mechanisms potentially related to some genes, might contribute to the desired therapeutic effect of ECT.

While genetic pathway alterations by ECT and their association with clinical parameters could provide pivotal information, few studies have examined the genetic approaches to neurobiology of ECT and the impact of pharmacogenomics on treatment response in ECT (Table 1). [68-74] These studies have shown that chronic molecular effects induced by ECT are more likely to reveal the mechanisms of its therapeutic effects.

A. Gene expression signatures

Studies have suggested that the therapeutic effects of ECT might be due to mechanisms involving several amino acid transmitter changes in brain through overexpression of their regulatory genes. Altar et al. investigated the effects of single versus repeated electroconvulsive seizure (ECS) exposure on gene transcription, in an animal model, to identify genes and potential biochemical pathways that are associated with the efficacy of chronic ECT. [55] Almost one hundred and twenty hippocampal and frontal genes were differentially expressed within distinct pathways (particularly BDNF-MAP kinase) in response to acute and chronic ECS. Of those, only nineteen genes showed similar expression in response to acute or chronic ECS. *B*rain-*D*erived *N*eurotrophic *F*actor (BDNF), cyclooxygenase (COX)-2, neuronal activity-regulated pentraxin (Narp), and TGFβ-inducible early growth response had co-directional changes in both brain regions. They suggested that the genes that increase only with chronic ECS are more likely to be associated with efficacy of ECT, including those of the BDNF-TRKB-MAP kinase pathway, arachidonic acid pathway, vascular endothelial growth factor (VEGF), thyrotropin-releasing hormone (TRH), neuropeptide Y (NPY), and regulators of neurogenesis. [55]

To address the therapeutic efficacy of ECS, Newton and colleagues examined the expression of neutrophins and related signaling pathways in the hippocampus of rats in response to ECS using a custom growth factor microarray chip. They reported the regulation of several genes that are involved in growth factor and angiogenic-endothelial signaling, including neuritin, stem cell factor, VEGF, (VGF), COX-2, and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1). [75] Some of these, as well as other identified growth factors, including VEGF, fibroblast growth factor, and BNDF, have effects on brain neurogenesis and cell proliferation. They also examined gene expression in the choroid plexus and found several enriched growth factors

in this vascular tissue, which were affected by ECS. Among the identified genes, TIMP-1 and COX-2 were highly expressed in both acute and chronic ECS. The authors suggested that the simultaneous augmented growth factor signaling with angiogenic process could have an important role in the mechanism underlying the therapeutic effect of ECT.

B. Single gene approach: expression or polymorphism based

In this approach a prior knowledge or presuppositions on a gene which directly or in directly may play a role in neurobiological mechanisms involved in efficacy of ECT response was used for investigation.

DARPP-32

DARPP-32 protein (dopamine- and cyclic-AMP-regulated phosphoprotein of molecular weight 32,000) has been of interest due to its phosphorylation regulation by dopamine and cAMP in nerve, which might mediate some dopamine effects. [76] *DARPP-32* gene down-regulation has also been implicated in schizopherenic patients. [77] Accordingly, Rosa et al. showed that *DARPP-32* expressions in striatum and hippocampus of rats increased after five ECSs in 48 hours. However, the effect was fluctuant and transient. [78]

COMT and APOE

Catechol-*O*-methyltransferase (COMT*),* a major enzyme in dopamine metabolism in the prefrontal cortex has been of interest in response to efficacy of ECT. Anttila et al. showed that *COMT* high-high genotype carriers would be more common in responders to ECT than other genotype carriers. [72] A finding that suggested the lower dopamine levels in the prefrontal cortex could be associated with substantially better treatment effects of ECT. COMT Val158Met, a functional polymorphism of *COMT* at codon 158 substantially affected the dopaminergic activity such that the Met allele homozygosity resulted in considerable reduction of enzymatic activity compared with the Val allele homozygosity. [72]

Domschke et al., in further investigation on val158met *COMT,* proposed that the impact of the SNP on the efficacy of ECT in depressive patients could be gender-specific. They also suggested that the val158met carrier might be less pharmacologically responsive to antidepressant and could benefit from ECT in their earlier stage of mood disorder. [79]

DRD2 and mutual effect with COMT

Huuhka et al. investigated the synergistic effect of two polymorphisms of Dopamine 2 receptor gene (DRD2) and *COMT*, C957T (rs6277) and Val158Met (rs4680) in response to ECT treatment. The study groups consisted of 118 depressive patients and 383 healthy controls. [13] They showed that had MT Met allele and *DRD2* T allele had synergistic effect in prediction of severity of depression. Furthermore, they found that the patients with TT

Table 1. The pharmacogenetic studies related to the outcome of ECT in animal and human subjects.

Author	Journal/year	Subjects	Procedure	Outcome measure	Author's conclusion
Nibuya et al. [111]	*J Neuroscience/1995*	Male rats	Single and 10 daily ECS	Northern blot analysis of BDNF and TRKB mRNA expression	BDNF and TRKB mRNA expression increased by chronic ECS in frontal cortex
Zetterstrom al.[112]	*Brain Res Mol Brain Res*	Male Rats	Single and 5 ECS over 10 days	Densitometric quantification	Both acute and chronic ECSs increased BDNF mRNA expression in brain, markedly in the granule cell layer of the dentate gyrus.
Fochtmann et al.[2]	*J ECT/1998*	Male rodents	Suprathreshold electroconvulsive seizures (ECS)	Correlations between hippocampal A1-receptor binding, cortical and striatal N-methyl-D-aspartate (NMDA)-receptor binding, and the modification of seizure duration by caffeine.	Quality of seizure could be influenced by heritable factors which might affect the neurobiologic mechanisms
Newton et al.[75]	The Journal of neuroscience/2003	Male rats	ECS treatment	Microarray analysis on several genes involved in growth factor and angiogenic-endothelial signaling, including vascular endothelial growth factor (VEGF)	Growth factor and angiogenic signaling have modulating role in could response to treatment by ECS.
Altar et al. [55]	Journal of the Society for Neuroscience/ 2004	Rats	ECS treatment	Gene transcription induction measurement in the frontal cortex and hippocampus.	Acute and chronic ECS induces differential expressions of several regulatory transcripts (e.g. BDNF) in brain. Subset of these transcripts shows similarity by time and region.
Rosa et al. [78]	Brain research	Rats	Single ECS treatment 8 ECS treatments	Measurement of DARPP-32 expression in time series	Chronic application of ECS increases DARPP-32 levels in striatum and hippocampus.
Voleti et al.[99]	Biological psychiatry /2012	Male rats	10 ECS treatments	Microarray analysis to identify cAMP-response element binding (CREB) promoters that are influenced by chronic ECS	Chronic ECS causes CREB dependent increase of Fz6 mRNA levels
Segawa et al.[89]	*The international journal of neuropsychopharmacology /2013*	Rats	Single and 10 day administration of ECS	Measurement of hippocampal levels of pro-BDNF, prohormone convertase 1 (PC1) and tissue-plasminogen activator (t-PA)	Induction of BDND expression is involved in therapeutic response to ECS.
Taliaz et al.[88]	*Biological psychiatry 2013*	Male rats	ECT for 10 days	BDNF measurement by enzyme-linked immunosorbent assay in knockdown rats for *BDNF* in hippocampus or ventral tegmental area (VTA) after ECT	ECT significantly reduced VTA BDNF expression causing antidepressant-like effects.

Bocchio-Chiavetto et al.[74]	*The journal of the European College of Neuropsychopharmacology/ 2006*	Patients with TRD-MDD with serial ECTs	ECT treatments (three times a week)	Serum BDNF levels at ECT time (T0), after ECT (T1) and one month after End of ECT (T2)	Serum BDNF levels increases by chronic application of ECT.
Huuhka et al.[13]	*Neuroscience letters/ 2008*	118 (F/M: 64/ 54) white patients with treatment resistant MDD treated with ECT vs. 383 healthy controls.	ECT treatments (three times a week)	MADRS <8 as responders, subjects were genotyping by using Taqman®SNP Genotyping Assay for Dopamine 2 receptor gene (DRD2) and COMT polymorphism	TT genotype of DRDD2 C957T polymorphism has synergistic effect with COMT gene polymorphism Met/ Met genotype and is was associated with less remission rate after ECT.
Huuhka et al.[69, 71]	*The journal of ECT/2005 and Neuroscience letters/2008*	118 (F/M: 65/ 54) white MDD patients	ECT treatments (three times a week)	MADRS <8 as responders, RGS4 and APOE genotyping was performed by using fluorogenic allele-specific TaqMan probes and primers	APOE and RGS4 genotype are not associated with ECT response in depression.
Anttila et al.[72]	*The pharmacogenomics journal/ 2008*	119 treatment resistant MDD patients (F/M: 65/54)	ECT treatments (three times a week)	Montgomery and Åsberg Depression Rating Scale (MADRS)<8 as responders, patients' DNA samples were genotyped by the 5′ exonuclease assay.	*COMT* high/high genotype carriers are more likely to respond to ECT (OR: 4.366 (95% CI: 1.137–16.770; *P*=0.023)
Stewart et al.[100]	*Neuroscience letters /2009*	119 treatment-resistant MDD with 392 controls	ECT treatments (three times a week)	Change in MADRS as the measure of treatment efficacy, to compare the effects of the angiotensin I-converting enzyme gene (ACE) genotype distributions and treatment response to ECT	ACE genotype is not associated with ECT outcome in depression but might be associated with age of onset
Domschke et al.[79]	*American journal of medical genetics/2010*	104 white TRD-MDD patients (F/M: 71/33)	ECT treatments (three times a week)	Hamilton depression rating scale (HAM-D) change > 50% baseline as responders, the effect of the COMT val158met polymorphism on ECT response	COMT gene variation might affect the response to ECT
Gedge et al.[113]	*Front psychiatry/2012*	29 TRD-MDD patients	One ECT session	BDNF and rTMS serum levels by ELISA; 1 week pre and post-ECT	ECT did not increase serum levels of BDNF or rTMS
Dannlowski et al.[80]	*The international journal of neuropsychopharmacology/2013*	104 white patients with treatment resistant MDD (F/M: 71/33)	ECT treatments (three times a week)	Ventral striatum responsiveness to happy faces by means of functional magnetic resonance imaging, the effect of the DRD3 polymorphism on ECT response	rs3732790, rs3773679 and rs9817063 variants are associated with ECT response and remission.
Viikki et al.[91]	*Psychiatric genetics/2013*	119 treatment resistant-MMD patients	ECT treatments (three times a week)	Change in MADRS, testing the association of two BDNF polymorphisms, rs11030101 and rs61888800	rs11030101 is associate with the efficacy of ECT.

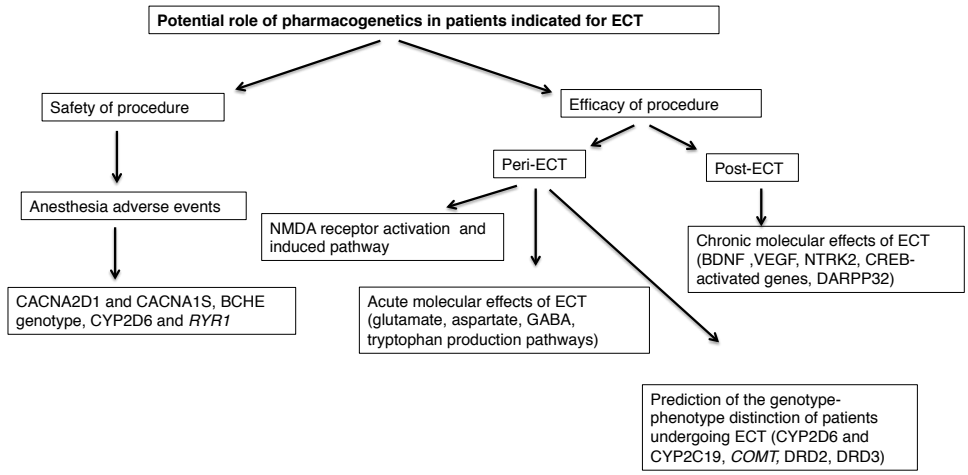

Figure 1. Various implications of pharmacogenetics in safety and efficacy of ECT

genotype of DRD2 C957T SNP and Met/Met genotype of *COMT* were less likely to reach remission than those with CC genotype of *DRD2* C957T and Val/Val genotype of *COMT*. Accordingly, they suggested the combined effect of these polymorphisms might be associated with response to ECT. [13]

APOE and RGS4

Huuhka et al. also examined the apolipoprotein E (*APOE*) well known for its association with neurodegenerative diseases as well as *RGS4* in prediction of TRD-MDD and found no association between *APOE* and *RGS4* polymorphism and response to ECT. [69, 71] This finding was, however, not consistent with the only previous study on the association of *APOE* and ECT responders. [68]

DRD3 (DR3)

To follow up on the role of dopamine D receptor gene in efficacy of ECT and evaluate the potential impact of dopamine D receptor gene (*DRD3*) variation on ECT outcome in treatment-resistant major depression, Dannlowski and colleagues used 10 genetic markers with high coverage percentage on *DRD3* to investigate the association with response to ECT in 104 treatment-resistant MDD white patients. They found significant association of rs3732790, rs3773679 variants of *DRD3* with response to ECT (p=0.02 and 0.03, respectively) and rs9817063 SNP with remission (p=0.01) after ECT. They suggested that *DRD3* gene variation might affect the efficacy of ECT that might potentially be mediated through neurobiological pathways of striatal activity. [80]

BDNF

BDNF is a member of the nerve growth factor family of neurotrophins. BDNF has been shown to exert important functions in neuronal survival, proliferation, and synaptic plasticity in the brain. [81-84] There are several biological evidences to support the role of BDNF as a central neurotrophic factor in the efficacy of ECT. These evidences have shown the inductive effects of both single and repeated ECT on BDNF secretion in brain that are reflective of BDNF changes in serum. [55, 74] Similarly, BDNF levels are shown to decrease in individuals with depression and increase following antidepressants; the changes that correlates with the severity of the disorder. [55, 85] Accordingly, it has been suggested that BDNF may at least in part explain both the acute and chronic potent effects of ECT in depressive disorders. [74, 86]

The neurobiological mechanisms of action in ECT have been proposed to be involvement in, the induction of BDNF secretion by prolonged increase of both *BDNF* and TRKB (*NTRK2)* mRNA expression in the hippocampus and entorhinal cortex (EC). [87] However, Taliaz et al. suggested that while neuroplastic alterations, as expressed by changes in BDNF expression within different brain regions, might be induced by ECT, the antidepressant-like effect of ECT in an animal model depends on reduction of the ventral tegmental area (VTA) *BDNF* expression but not on the elevation of hippocampal *BDNF* expression. [88]

In an animal experiment, Segawa and colleagues tried to explain the role BDNF and pro-BDNF in acute and chronic ECT treatment. They found that single administration of ECS rapidly increased hippocampal levels of pro-BDNF along with levels of prohormone convertase 1 (PC1) and tissue-plasminogen activator (t-PA). These two proteases are involved in intra- and extracellular pro-BDNF processing. [89] Further ECSs resulted increase hippocampal level of pro-BDNF as well as mature BDNF level. Taken together, they suggested that while PC1 and t-PA could both be involved in pro-BDNF processing connected with acute antidepressant effect of ECT, t-PA might play a dominant role following repeated ECS. [89] In their model, chronic administration of imipramine significantly increased mature BDNF levels, but not pro-BDNF and protease levels, indicating that the therapeutic mechanism of antidepressants might differ from that of ECT.

Clinical studies support some of the obtained evidences by pre-clinical studies on BDNF. The significant increase in serum levels of BDNF has been detected in patients undergoing chronic ECTs. [74] A possible mechanism for this observation has been proposed to be due to *BDNF* gene upregulation mediated by histone H3 and H4 acetylation [90], though in pre-clinical setting. Viikki and colleagues, in a recent study of 119 depressive patients, investigated the association between *BDNF* polymorphism rs11030101 and the efficacy of ECT. Their study demonstrated that the TA genotype carriers of rs11030101 were less likely to show

improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) and benefit from ECT compared with patients with the TT genotype. [91]

VEGF, P2RX7 and HTR2A

Viikki et al. also examined the association between the *VEGF* 2578 C/A polymorphism and ECT in of 119 patients with TRD who were treated with ECT and 98 depressive patients treated with SSRIs compared to healthy controls. According to their findings, the CC genotype of *VEGF* 2578C/A polymorphism was more common in patients treated with ECT and SSRI than in healthy controls (31.1%, 25.5% and 18.7% respectively; p=0.056). The VEGF 2578 C/A polymorphism was associated with treatment resistant depression and CC genotype was more frequent in patients underwent ECT than in controls (31.1% and 18.7% respectively; p=0.015). [92] In the same study groups, they investigated the rs2230912 and rs2230912 *P2RX7* polymorphisms. Neither of these two *P2RX7* SNP was associated with either remission after SSRI or ECT. [93] In the same study populations, they investigated the improvement of depression using MADRS score after ECT in association with rs7997012 and rs6311 *HTR2A* polymorphisms. None of the SNPs were associated with the change in MADRS score due to treatment. However, the interaction between the SNPs and gender explained 14% of the variance in MADRS score change. [94]

CREB

Fizzled 6 (FZ6) is a seven transmembrane-spanning receptor involved in Wnt signaling. This signaling pathway is one of the essential mechanisms in cell proliferation, polarity and fate determination during embryonic development and tissue homeostasis. [95, 96] The main signaling pathway is activated by FZ/β-catenin, FZ/Ca^{+2} and FZ/planar cell polarity signaling pathways [97] and inhibited by Dickkopf (Dkk) family members (e.g. Dkk1 which functions as secreted Wnt antagonists by inhibiting Wnt coreceptors LRP5/6). [98] Voleti et al. demonstrated that chronic administration of ECS augments the activity of several hippocampal genes through the cAMP-response element binding (CREB) such that subsequent effects might lead to the effectiveness of chronic ECT. FZ6 was also one of CREB-target genes, which was affected by chronic ECS. In their study, viral vector-mediated inhibition of Fzd6 produced anxiety and depressive-like effects. [99] Accordingly, the authors suggested that the activation of CREB might have regulatory effect on multiple functional pathways such that the therapeutic effect of ECS is dependent on a particular set of CREB-activated genes. [99]

ACE

The angiotensin I-converting enzyme gene (ACE) has been suggested as a major gene affecting affective disorders and their treatment. To compare the effects of the ACE genotype distributions and treatment response to ECT in MDD patients, Stewart et al. studied 119

treatment-resistant depressive patients who were referred for ECT. All participants were genotyped for *ACE,* and the efficacy of ECT was evaluated using the MADRS. ACE genotype was not associated ECT efficacy and did not show a different frequency with healthy controls. [100]

Discussion and future perspective

Our review demonstrates that the knowledge for safe application of ECT treatment of major depression and other psychiatric disorders has been improved, at least partly due to the role of pharmacogenetics in application of anesthetic agents. Some genes such as *CACNA2D1* and C*ACNA1S*, *BCHE* and *RYR1* are associated with safe practice of anesthesia in ECT. While our review demonstrates that at this point, the knowledge of the mechanisms underlying the efficacy of ECT has not been thoroughly elucidated, we identified several genes (i.e. *BDNF, COMT, DDR2, DDR3, CREB, VEGF, COX-2, TRKB* and *NMDA receptor*), which their transcriptions might play important role in treatment response to ECT. It is important to identify the neural and the molecular pathways related to these that might explain the mediation of the behavioral changes by ECT and its timely application.

An ideal shock treatment produces two sets of acute and chronic neurobiological responses that result in a rapid and sustained treatment response for treatment of psychological disorders. Accordingly, Altar et al.'s experiment showed that the neurobiological mechanisms during ECT substantially differ by chronicity. More importantly they showed that a subset of genes would continue to be similarly expressed in some brain regions by both acute and chronic ECT. This fact could be suggestive that efficacy of ECT could be due to some common regulatory pathways modulated by the therapeutic stimulus. Investigating the potential brain regulatory network pathways among the abstracted genes (*BDNF, COMT, DDR2, DDR3, CREB, VEGF, COX-2 and TRKB*), we identified that all genes or their transmitters are co-expressed as part of transcriptionally regulatory sub-networks in brain, more prominently in the frontal lobe (Figure 2 & 3). In these sub-regulatory networks, AP-1 transcription including CREB demonstrates the most regulatory effects on the network objects. This takes on greater significance that effectiveness of ECT is more dependent on treatment response to its chronic application. Consistently, Hope et al. [101] showed AP-1 complex had high expression by administration of chronic ECT and persisted to be highly expressed by 7 days after the last ECT. It has been shown that AP-1 modulation affects many cell processes including cell proliferation, differentiation, transformation, neuronal activity and growth factor signaling. [102, 103] More importantly, it has been suggested that AP-1 could act as an environmental biosensor in mediating the linked cellular biological process. [102]

There are other factors that might affect the variations in expression levels in brain regions

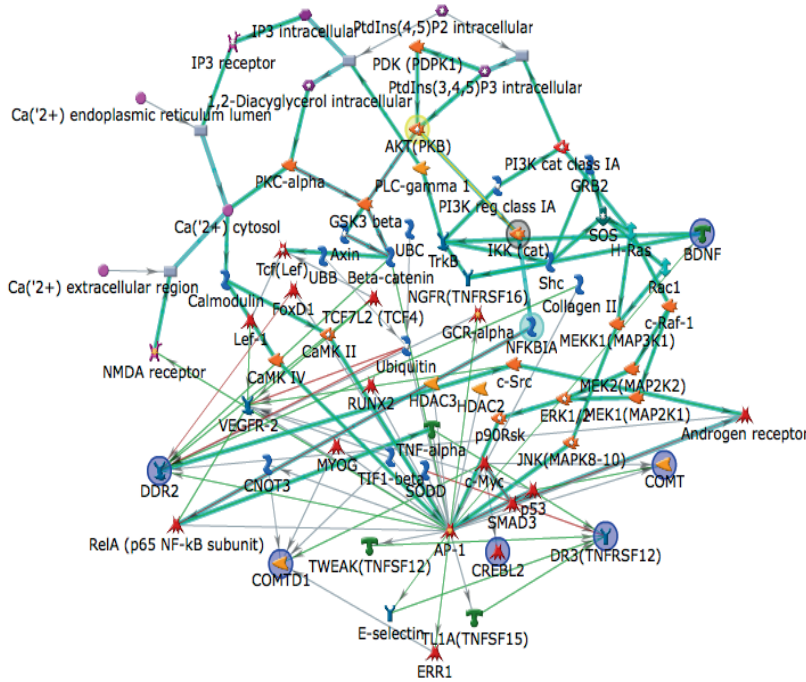

Figure 2. The demonstration of regulatory pathways among BDNF, COMT, DDR2, DDR3, CREB TRKB, and NMDA receptor in human brain. AP-1 complex shows the most regulatory effect on the genes of interest. Green arrows demonstrate activation and red arrows deactivation.

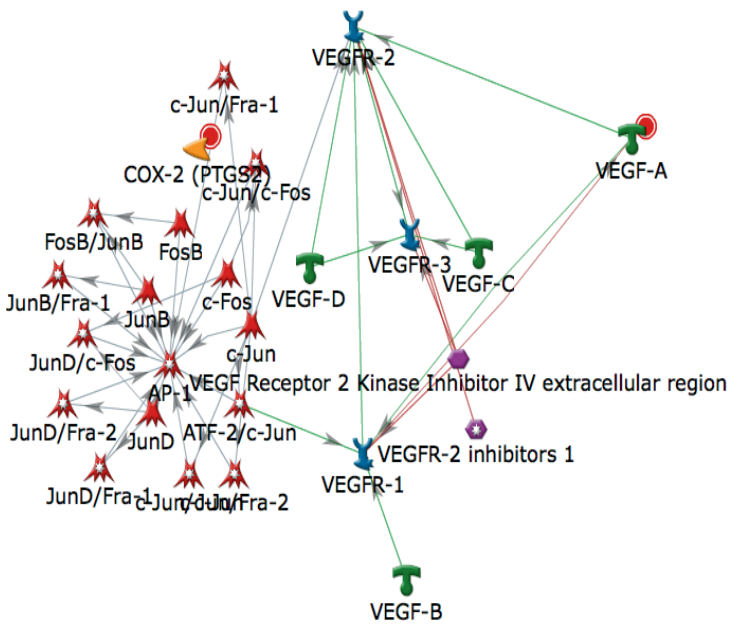

Figure 3. The demonstration of regulatory pathways among AP-1 complex, Cox2, and VEGF in human brain.

and directionality of regional regulatory networks. For example, there is evidence of variations in activity level of *BDNF* transcripts in different brain regions [88, 104] or other patients' clinical characteristics such as gender might influence some observed gene polymorphisms in response to treatment. [94]

In spite of all the improved knowledge on the safety of ECT and its proved efficacy in treatment of some psychiatric patients unresponsive to medical therapy, ECT is still a physical intervention and more cumbersome than medications with higher efficacy. Accordingly, our understanding the acute and chronic molecular, cellular, and behavioral changes by ECT will provide a new view to find potential targets for novel psychotropic treatments, particularly antidepressants, that are highlighted by the findings such as regional gene induction (e.g. *BNDF*, *Cox-2*), increased neurogenesis, electrophysiological reactivity, the role of VEGF in neurogenesis, [105, 106] and *DARPP-32* expression. [78] Some genes and associated pathways such as BDNF, TRKB-MAP kinase pathway, NPY, VEGF, arachidonic acid pathway, TRH, VEGF, and neurogenesis regulation pathways, which have shown differential expressions due to chronic stimulation by ECT, are more probable to have an intermediary role in benefiting from the long-term effects of ECT. These evidences along with shared regulatory pathways such as AP-1 and CREB could be useful for further investigation to identify novel gene targets for treating treatment resistant psychological disease.

Palfreyman et al. suggest illustrating a "disease signature" and "drug signature" of aberrantly expressed genes from comparison of normal controls and patients. [107] In this approach, the genes associated with disease will be explored. The comparison of the soptted genes with ECT signature genes could identify a set of targets whose alteration might be a better predictor of disease and the effect of procedural treatment. Ultimately, such overlapping genes could be used to identify drug compounds that show similarity in inducing the gene expressions, which consequently mimic the therapeutic response of ECT. This method has been applied in animal mode such that [108] several compounds have been investigated to identify the one that alter the same eleven genes elevated by ECT or exercise in rat brain. Of note, exercise has been favorably compared to antidepressant treatment for treatment of mild to moderate depression. [108-110] Such compounds could also be used to augment the induced differentially genes expressions by chronic exposure to ECT or by antipsychotics. [55] Further well-designed longitudinal clinical studies are required to increase our knowledge of the mechanisms underlying the efficacy of ECT.

Executive summary

Pharmacogenetics and safety of ECT

I. Anesthesia adverse events

Abnormalities in butyrylcholinesterase

- BCHE deficiency could result in a prolonged effect of the ultra-short acting depolarizing succinylcholine, the muscle relaxant of choice ECT, due to markedly decrease in plasma cholinesterase activity.

- Succinylcholine duration of action is prolonged for the patient with heterozygous for the K-variant allele, the most frequent variant.

Malignant hyperthermia

- Approximately 50% of MH related genetic variants have been found in the *RYR1* gene on chromosome 19.

- Most cases (70%) harbor one of 30 *RYR1* mutations.

- *CACNA2D1* and *CACNA1S* variants account for less than 2% of cases and the causal genetic variant in approximately 30% of patients is unknown.

- The reported incidence of MH during ECT has been less than other procedures requiring general anesthesia.

Neuroleptic malignant syndrome

- *CYP2D6* polymorphism, the enzyme through which most psychotropic drugs are metabolized and TaqIA DRD2, a target for antipsychotic drugs, has been suggested the link between pharmacogenetic factors and the potential development of NMS.

- In spite of these genetic links, reliable NMS during ECT has been reported.

II. Potential neurobiological mechanisms in cognitive side effects of ECT

- ECT-induced cognitive disruption might be mediated by glutamate at N-methyl-d-aspartate receptors.

  - Using Ketamine as anesthetics during ECT might result in less impairment of short-term memory

- Higher basal level of cortisol might be associated with greater degree of ECT-induced cognitive impairment.

- Acute effect of ECT causes perturbations of several amino acid transmitters and the brain biomarkers in blood with might be associated with neuronal activity or potential neuronal injury.

Pharmacogenetics and the efficacy of ECT

The effect of adjunctive psychotropic drugs on ECT outcome

- The current remission rates after ECT appear to have declined

  - The overall remission rate has been reported to be 48.0% and 64.9% patients with and without previous pharmacotherapy failure, respectively.

- ECT has shown higher efficacy in conjunction with antidepressants and antipsychotics

- Application of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine during ECT might augment rapid and longer antidepressant effect of ECT.

  - NMDA receptor antagonism could activate mammalian target of rapamycin (mTOR) and *B*rain-*D*erived *N*eurotrophic *F*actor (BDNF) pathways.

Potential pharmacogenomics/neurobiological mechanisms in the efficacy of ECT

I. Brain Alterations in Acute and chronic ECT response

- ECT affects wide range of brain areas.

- Therapeutic effects on brain regions may be through structural, and/or biochemical changes

- ECT could have similar effect like antidepressants in down-regulation of brain 5-HT_2 receptors in the limbic and prefrontal cortical brain areas.

- ECT could augment the increase in Dopamine D_2 receptors in some brain areas in patients who received ECT.

- ECT might effect on structural plasticity within dorsal fronto-limbic pathways and plasticity of WM relation to therapeutic response in depression

II. Potential genes involved in ECT response and the related biological pathways

A. Gene expression signatures

- Therapeutic effects of ECT might be due to mechanisms involving several amino acid transmitter changes in brain through overexpression of their regulatory genes.

- There are some similarities in ECT induced regional alterations, e.g. hippocampus and frontal lobe

- Several genes such as *VEGF, VGF, COX-2 and TIMP-1* involved in growth factor and angiogenic-endothelial signaling could be co-expressed by both acute and chronic ECT.

B. Single gene approach: expression or polymorphism based

- Several individual genes have been investigated in association with ECT efficacy.

- ECT could transiently increase *DARPP-32* expressions in striatum and hippocampus.

- The combined effect of *COMT and DRD2* polymorphisms might be associated with response to ECT. *COMT* high-high genotype carriers would be more common in responders to ECT than other genotype carriers.

- *DR3* rs3732790, rs3773679 SNPs are associated with remission after ECT.

- Both single and repeated ECTs increase BDNF secretions in mRNA expression, mostly in the hippocampus and entorhinal cortex.

  -The BDNF change in brain is reflective of changes in serum

  - PC1 and t-PA could both be involved in BDNF expression processing connected with acute antidepressant effect of ECT; t-PA might play a dominant role following repeated ECS

  - TA genotype carriers of rs11030101 was shown to be less likely to show improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) and benefit from ECT compared with patients with the TT genotype

- VEGF 2578 CC genotype was observed with more frequent in patients underwent ECT.

- *CREB* might have regulatory effect on multiple functional pathways such that the therapeutic effect of ECS is dependent on a particular set of CREB-activated genes.

Discussion and future perspective

- *BDNF, COMT, DDR2, DDR3, CREB, VEGF, COX-2, TRKB* and *NMDA receptor* are genes that their functions could affect the efficacy of ECT.

- The potential genes involved in efficacy of the ECT or their transmitters are co-expressed as part of transcriptionally regulatory sub-networks.
- In these sub-regulatory networks, AP-1 transcription including CREB could be a major regulator of the network objects.
- AP-1 complex has shown high expression by administration of chronic ECT and persists to be highly expressed by 7 days after the last ECT.
- The shared regulatory pathways such as AP-1 and CREB could be useful for further investigation to identify novel gene targets for treating treatment resistant psychological disease.
- Investigating ECT signature genes as compared to different drug compounds could help in identifying medications that might augment the induced differentially gene expression by ECT.
- Further well-designed longitudinal clinical studies are required to increase our knowledge of the mechanisms underlying the efficacy of ECT

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6

CYP2D6 Metabolizer Phenotypes in Patients Undergoing ECT After Antidepressant Therapy

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Pharmacogenet Genomics. 2015 Oct;25(10):515-7

ABSTRACT

Introduction

Major depressive disorder (MDD) and bipolar disorder (BD) are common mental disorders. According to present guidelines, the effective antidepressant for treatment of MDD and BD for each individual patient is identified through trial and error switching in sequential treatments. A substantial proportion of depressive patients do not benefit from treatment due to ineffectiveness of medication therapy or incurring serious side effects. *CYP2D6* variants are associated with metabolic profile of antidepressant and have been investigated as a determinant contributor in treatment resistant depression (TRD). Hereby, we investigate the accumulation of aberrant *CYP2D6* genotypes and predicted metabolizer phenotypes (UM, IM, and PM) potentially affecting the antidepressants treatment response in depressive patients indicated for electroconvulsive therapy (ECT) compared to patients with single episode of depression.

Method

84 Dutch Caucasian subjects with unipolar or bipolar treatment resistance depression who underwent ECT were genotyped using Amplichip® *CYP450* Genotyping Test for *CYP2D6* and its metabolizer phenotypes. 208 genotyped patients with single episode of unipolar or bipolar depression were used as controls to examine differences in prevalence of *CYP2D6* phenotypes.

Result

The mean age of ECT cases and subjects with single episode of depression was 62 ± 14 [range: 27-87, F/M: 46/29] and 49 ± 19 [range: 15-91, F/M: 91/117], respectively. Prevalence of *CYP2D6* phenotypes (PM, IM, EM and UM) was "5.3%, 38.7%, 56% and 0.0%"for ECT patients, and "6.4%, 51%, 42.6% and 0.0%" for depressive patients. The type of depression and age (*P*=0.018 [OR=0.33] and 0.001 [OR=1.05], but not *CYP2D6* phenotype were associated with the response to treatment.

Conclusion

The frequencies of genotype-predicted-phenotypes, potentially affecting the treatment response (UM, IM and PM), did not show increased frequency in patients who received ECT for continuation of depression treatment as compared to patients with single episode of depression. Preemptive genotyping for *CYP2D6* currently appears to have no clinical implications in treatment resistance depressive patients undergoing ECT. Further large-scale prospective clinical trials are warranted.

INTRODUCTION

Mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD), are common mental disorders and amongst the leading causes of disability worldwide. Currently depression is estimated to affect 350 million people [1] and according to the World Health Organization (WHO) MDD is the eleventh highest cause of disability-adjusted life years (DALYs) worldwide. [2]

While options for treatment include psychotherapy, pharmacotherapy and electroconvulsive therapy (ECT), in both moderate and severe MDD, as well as in BD, antidepressant agents are part of the mainstay of treatment in MDD and can be given in the form of single or multiple antidepressants. Patients diagnosed with BD suffer from recurrent depressions and manic episodes. Between episodes, many patients have a low mood characterized as 'sub-threshold depression'. In BD, mood stabilizers e.g. lithium are the first choice of treatment, and in the case of a bipolar depression, antidepressants may be added to the mood stabilizer. Numerous studies in MDD patients show comparable response rates across different classes of antidepressants [3]. Generally, in patients with insufficient response to a certain antidepressant, the drug dosage can be increased, augmenting drugs can be prescribed or a switch to another antidepressant can be made after an adequate (duration and dosage) trial. [4-6] When multiple treatment steps are required, lower acute remission rates and higher relapse rates during the follow-up phase are to be expected [5, 7]. In spite of the availability of multiple pharmacologic classes of medications and their sequenced trials using available guidelines for depression treatment, 50% of patients with major depressive disorder (MDD) fail to achieve complete remission. [8] ECT, as a non-pharmacological intervention, has been shown a favorable option in such cases of treatment resistant unipolar and bipolar depression [9-12] and could be an effective and relatively safe antidepressant treatment. ECT may, particularly, be a life saving treatment in the case of severe depression with psychotic or catatonic features. However, the level of pharmacoresistance that has to be reached until ECT may be applied is not clear. Although ECT is generally only administered after several medication trials have failed due to the invasiveness of the treatment including hospital admission, repetitive narcoses and possible side effects like cognitive disorders, guidelines indicate that ECT is always an option in severe MDD and bipolar depression. [13] Therefore, the indication for ECT is usually a clinical decision, and ECT patients in general reflect the severe range of the depression spectrum. [14]

Treatment related factors, including noncompliance and inadequate antidepressant use (duration and dosage), are determinants of treatment failure. [15] Though therapeutic drug monitoring for antidepressants is commonly available it is not always routinely applied. Any

plasma concentration of antidepressants below or above the therapeutic range may lead to ineffectiveness or side effects respectively, which in turn could result in poor response to treatment or noncompliance, in both MDD and BD. Consequently, adverse effects are common reasons for switching antidepressants, leading to more medication trials and a sense of medication "resistance." Genetic factors are important determinants in the variation of treatment response in depression disorders as well contributing to its etiology, course and prognosis [16]. The enzyme cytochrome P450 2D6 (*CYP2D6*) plays an important role in the pharmacokinetics of many antidepressants. The *CYP2D6* gene is extremely polymorphic, with over 100 alleles known, explaining part of the observed wide range of variability in CYP2D*6* catalytic activity among individuals [15] and consequently prominent contributor to interindividual drug response. [17-20] The *CYP2D6* genotype can be used to predict the phenotype of the enzyme, and four distinct phenotypes with increasing metabolic capacity are distinguished: poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM) and ultrarapid metabolizer (UM).

An evident relation between the phenotypes of the *CYP2D6* enzyme and the observed blood concentration of several antidepressants exists. [12] Determining an individual's *CYP2D6* phenotype, or metabolic status, will help identify those that are likely to benefit from modifications to pharmacotherapy. [17] This will improve the patient's experience and compliance with medications, which could decrease the number of trials needed to achieve remission and avoiding treatment resistance. Additionally the *CYP2D6* polymorphism may become more important as the use of different medications in patients with multiple comorbidities, particularly in the elders, might increase the risk for drug–drug interactions.

The purpose of our study is to investigate the prevalence of *CYP2D6* phenotypes in depressive patients who were indicated for ECT treatment as a rapid acting treatment and compared to patients with single episode of depression. Accordingly, we hypothesize that there is an accumulation of aberrant *CYP2D6* genotypes and consequent *CYP2D6* metabolizer phenotype(s) in patients undergoing ECT. Furthermore, we would like to investigate if the patients' characteristics such as age and gender might affect of the acquired association of phenotypes with patient who underwent ECT.

METHODS

Study protocol was exempt from obtaining approval by institutional review board of Leiden University Medical Centre due to the retrospective character of the study and the fact that all ECT patients had been routinely genotyped for *CYP2D6* as part of the local ECT protocol.

Patients

84 Dutch Caucasian subjects with unipolar or bipolar depression that received ECT for treatment of depression in the Department of Psychiatry at the Leiden University Medical Centre (LUMC) from July 2009 to June 2014 were included in the study. All the cases had at least one adequate trial of a major class of antidepressant, sensitive to genetic polymorphism of *CYP2D6*, at their current episode of depression and time of ECT trials. In addition, ECT cases had a history of concomitant therapy with several other antidepressants in their current or prior episodes and sequenced treatment trials, which satisfied the current unstandardized criteria for treatment resistant depression (TRD). [15, 21-27] Patients with bipolar disorder were also receiving a mood stabilizer such as lithium. The exclusion criteria were receiving non-*CYP2D6*-dependent antidepressants, not having reliable medical record on the current medication usage or meeting the inclusion criteria for being on adequate dosage/duration of antidepressants. Indications for ECT were failure of response to treatment (mostly due to treatment resistance depression or intolerability of treatment adverse effects) in unipolar and bipolar depressive patients for severe depression with psychotic features. All the medications and medical information of patients were collected from the psychiatric and medical histories available on CS-EZIS, the electronic patient record file system of LUMC comprised of multiple functional modules for clinicians and researchers.

For the control group, depressive patients (unipolar and bipolar) from mental health clinic GGZ Centraal, Amersfoort, the Netherlands were used. Using electronic patient record files from January 2006 to June 2014, 480 patients with a history of depressive episodes were identified and 208 subjects who had a single episode of unipolar or bipolar depression treated with antidepressants and without history of depression recurrence were screened as the control group.

Genotyping, Phenotype and activity score

Amplichip® *CYP450* Genotyping Test (Roche Diagnostic GmBH, D-68298 Mannheim, Germany) approved by the U.S. Food and Drug Administration (FDA) was used to detect the most common variant alleles of the *CYP2D6* gene in the ECT patients. The Amplichip performs genotyping of two Cytochrome P450 genes and provides the predictive phenotype of the associated enzymatic activities, using DNA purified from human blood. The assay distinguishes 29 known polymorphisms in the *CYP2D6* gene, including gene duplication and gene deletion. Detection of these *CYP2D6* polymorphisms results in the identification of 33 unique alleles, including seven *CYP2D6* gene duplication alleles. Control patients were genotyped for CYP2D6 *3, *4, *5, *6, *9, *10, *41 and gene multiplication as described previously. [28] Subjects were classified, according to their expected phenotype, into four groups of poor (PM), intermediate (IM), extensive (EM) and ultrarapid (UM) metabolizers

as follows: patients with two null alleles (**3, *4, *5, *6*) were classified as PM, patients with a null allele in combination with a deficient (**9, *10, *41*) or a functional allele (defined by the absence of any of the determined mutations), or with two deficient alleles were classified as IM, and patients with a gene duplication (xN) in absence of any of the determined mutations were classified as UM. Patients for whom no phenotype could be predicted, due to unknown identity of the allele multiplied, were classified as "unknown". We also used *CYP2D6* activity score system corresponding to each *CYP2D6* metabolizer categorizations. [17]

Adequate antidepressant therapy and treatment response assessment

In patients with unipolar MDD who underwent ECT for their current episode of depression, an antidepressant trial lasting at least 4 weeks at an optimal dose of the prescribed antidepressant (at least as high as the lowest dose defined as effective in the package insert) for the current or the most recent episode of depression was considered as an adequate treatment for inclusion in the study. [22-25] For bipolar depression, similar criteria of treatment-resistance were used with the provision that failure to respond to antidepressant(s) was along with at least one adequate mood stabilizer in the current depressive episode. [29]

Patients' clinical courses (severity of depressive episodes) and response failure to treatment were validated by the Montgomery-Åsberg Depression Rating Scale (MADRS) [30] prior to ECT trials. The cut-off score of more than 10 was considered as treatment ineffectiveness, indicating patients who were not in remission under current antidepressant trial. [13, 31]

Statistical analysis

Data are presented as Mean ± SD [range]. All the calculations were performed using "SPSS Statistics for Windows, Version 20.0 (Armonk, NY: IBM Corp., USA, IBM Corp. 2010.

A chi-square test of independence was performed to examine the relation between *CYP2D6* phenotypes with patients who indicated for ECT (cases) and patients with single depressive episode (controls). Binary regression, was applied to test if the result of the association of *CYP2D6* phenotypes with patient groups would be affected by the adjustment of variables of age, sex and unipolar vs. bipolar depression.

RESULTS

After exclusion of eight ECT patients due to exclusion criteria, a total of 76 ECT candidate patients meeting the DSM-IV criteria for a unipolar or bipolar depressive episode disorder who met the inclusion criteria were assessed. Patients with bipolar disorder had adequate mood stabilizer for their current depressive episode resulting in ECT trials as well as an

optimal dose and an adequate antidepressant treatment. The mean age of ECT cases and subjects with single episode of depression were 62 ±14) [27-87, F/M: 46/29] and 49 ±19 [15-91, F/M: 91/117], respectively (Table 1).

Table 1. Patients' clinical characteristics and CYP2D6 phenotype distribution and activity score.

Age, Mean (SD) [range]	62 (14)[27-87]	49 (19) [15-91]
Sex (F/M)[a]	46/29	91/117
Unipolar/bipolar depression	64/12	196/12
CYP2D6 activity score		
Range	0-2	0-2
Median	1.5	1
0-0.5 (%)	10	16
1-2 (%)	90	84
CYP2D6 phenotype (%)[b]		
PM	5.33	6.44
IM	38.67	50.99
EM	56	42.57
UM	0	0

[a]F: female, M: male; [b]PM: poor metabolizer, IM: intermediate metabolizer, EM: extensive metabolizer, UM: ultrarapid metabolizer

Prevalence of CYP2D6 phenotypes and activity score

The prevalence of *CYP2D6* phenotypes (PM, IM, EM and UM) was "5.3%, 38.7%, 56% and 0.0%" and "6.4%, 51%, 42.6% and 0.0%"for ECT patients and depressive patients respectively. The relation between patients groups and *CYP2D6* phenotypes (UM excluded due to frequency of 0.0%) were not significant (χ_2 [df=2, N = 282] = 3.99, *P* =0.136). Median of *CYP2D6* activity scores in ECT patients vs. patients with single episode of depression was 1.5 and 1, respectively.

Adjustment of the association of CYP2D6 phenotype for patients' characteristics

A logistic regression analysis was conducted to investigate the association of covariates (type of depression [unipolar vs. bipolar], age, sex, *CYP2D6* phenotype and activity score) with cases that were indicated for the continuation of their treatment using ECT.

A test of the full model against a constant only model was statistically significant, indicating that some covariates included, conditioned on others, were associated with patient groups (chi square= 39.12, *P*<0.001 with *df*=4*).* The Wald criterion demonstrated that the type of depression and age (*P*=0.018 and *P*= 0.001, respectively), but not the *CYP2D6* phenotype (PM/EM, *P*=0.29), were associated with receiving ECT. Sex and activity score neither were significant contributor to the outcome of treatment (*P*=0.57 and *P*=0.174). Odds ratio (OR) values of age and unipolar depression were 1.05, 0.33, respectively (Table 2). After

adjustment for age, gender, and type of depression, *CYP2D6* phenotype IM compared to EM was associated with patients who were treated with ECT (OR=0.53, *P*=0.03).

Table 2. Adjusted frequencies of CYP2D6 phenotypes and activity score by type of depression (unipolar vs. bipolar), age and sex.

Age	1.05	1.03-1.06	25.1	<0.001*
Unipolar/bipolar depression	0.33	0.13-0.83	5.6	0.018*
Sex (M/F)	0.84	0.47-1.5	0.32	0.55
CYP2D6 phenotype				
EM: Reference			5.47	
PM	0.49	0.12-1.7	1.14	0.29
IM	0.53	0.3-0.96	4.33	0.04*
CYP2D6 activity score				
Low (0-0.5)/High (1-2)	0.55	0.21-1.12	1.87	0.17

[a]F: female, M: male; [b]PM: poor metabolizer, IM: intermediate metabolizer, EM: extensive metabolizer)

Table 3. Frequencies of *CYP2D6* alleles and the predicted CYP2D6 phenotypes in patients indicated for ECT due to antidepressant treatment failure.

*4/*4Xn	0	PM	1
*1/*1	2.0	EM	14
*1/*2	2.0	EM	9
*1/*9	1.5	EM	5
*1/*35	1.5	EM	4
*1/*41	1.5	EM	7
*2/*41	1.5	EM	4
*1/*3	1.0	IM	1
*1/*4	1.0	IM	10
*1/*5	1.0	IM	3
*2/*3	1.0	IM	1
*2/*4	1.0	IM	3
*2/*5	1.0	IM	1
*2/*9	1.0	IM	1
*4/*35	1.0	IM	3
*5/*35	1.0	IM	1
*5/*41	1.0	IM	1
*6/*41	1.0	IM	1
*9/*41	1.0	IM	2
*4/*9	0.5	IM	1
*3/*5	0	PM	1
*4/*4	0	PM	2

DISCUSSION

This study investigated the frequency of the recognized *CYP2D6* phenotypes among patients who had single episode of depression or indicated for ECT due to non-response to treatment for unipolar or bipolar depression or adverse effects to antidepressants. Frequency of UM, IM and PM *CYP2D6* phenotypes were not associated with failure of antidepressant treatment response, i.e. patients who underwent ECT for their continuation of treatment. In another study, Haber et al.'s demonstrated that Hungarian patients with difficult-to-treat depression (N=55) did not exhibit an increased frequency of aberrant *CYP2D6* phenotypes [32] compared to the healthy subjects' *CYP2D6* phenotypes. In our study, the observed allele frequency of UM was 0.0% as opposed to the previously reported frequency of 0.01 in Dutch population (prevalence of 4.5%). [33] Prevalence of *CYP2D6* PMs has been estimated to be 5.5%-9% [34-36] in healthy Dutch volunteers. Consistent with these estimations, the prevalence of PMs in ECT patients and patients with single episode of depression were 5.3% and 6.4%, respectively. The frequencies of IMs in both ECT patients and those with single episode disorders of depression were higher than healthy subjects, [36] such that, after adjustment for other factors, the odds of patients with depression eventually treated by ECT was lower, if they had *CYP2D6* IM phenotypes.

Several studies [37] have demonstrated that poor *CYP2D6* metabolizers have a higher incidence of adverse effects when taking *CYP2D6*-dependent antidepressants and more risk of TRD. [38-42] Laika et al [43] reported that intermediate *CYP2D6* metabolizer status on therapeutic outcome in 365 psychiatric in-patients treated with neuroleptics or antidepressants was associated with delay onset of response to treatment and increased length of hospitalization for patients receiving *CYP2D6*-dependent drugs. They also reported that patients with *CYP2D6* IM phenotypes receiving *CYP2D6*-dependent drug doses above the population median had more side effects after 4 weeks than extensive metabolizers. However, an almost equal number of studies did not find significant evidence to support previously mentioned studies on the effect of IMs and PMs over EMs related to occurrence of nonresponse in psychiatric patients treated with antidepressants. [44-48]

Similarly, several studies have reported an association between ultra-rapid *CYP2D6* metabolizer status and diminished response to antidepressants, [41, 49, 50] but no association was shown in a larger retrospective study. [51] Of note, most these studies are in different population witch represent different allele frequencies of *CYP2D6* phenotype. [33] Despite of the equivocal evidences, the current recommendations for standard doses gives consideration for extreme phenotypes of PMs and UMs. It has been suggested that standard drug dose may not result in therapeutic plasma levels for UMs and may increase the risk of an adverse drug reaction and consequent therapeutic failure in PMs. [33, 41, 52-54] Therefore,

it is proposed that lack of response in EMs (and UMs) could be overcome with the dose escalation of antidepressants, while a compound switch might be more promising in PMs to avoid unresponsiveness to treatment or drug adverse effects. [55] As such, prior knowledge of *CYP2D6* metabolizer phenotypes and therapeutic monitoring might reduce the risk of non-responsiveness to the *CYP2D6*-dependent antidepressants [56] and indication of ECT, at least at earlier stages of treatment of depression. Nevertheless, a routine application of *CYP2D6* genotyping prior to treatment is under debate and our study is not conclusive for such recommendation.

This study further sought to identify possible effect of age, gender and type of depression in prediction of response treatment. While some studies have shown a better response to antidepressants (particularly to SSRIs) among women [57, 58], our data is consistent with Parker and et al.'s finding that women did not show a preferential response to SSRI medication [59]. The failure of gender to be associated with the depression recurrence has also been investigated in larger, epidemiological samples and a multicenter trial. [60, 61] Future studies should consider investigation in potential differences of metabolic ratio among *CYP2D6* phenotypes between women and men [35] in response to antidepressants.

The influence of age of onset on outcome in antidepressant trials is controversial [62]. Our data shows that patients who indicated for applying ECT for the treatment of resistant and recurrent depression were older than patients with single episode of depression. In a long-term randomized clinical trial study by Frank et al. [63], no such association was found. However, previous observations showed that both early onset of depression (<40 years old) and late onset (>50 years old) are associated with a higher risk of depression recurrence. These conflicting results might be explained by the fact that late-onset data have been obtained in clinical populations [64, 65], as compared to early onset of depression and higher risk of recurrence in a nonclinical population [66]. Giles and colleagues showed that only age at onset was significant in predicting a recurrent episode. [67] Lewinsohn and colleagues [68] also demonstrated that a *later age of first episode of depression* was associated to faster recurrence.

Additionally, our data suggests that patients with bipolar depression might have higher risk of receiving ECT as treatment for bipolar depression than those with unipolar depression (odds ratio of 3.0). Relevantly, Ghaemi and colleagues [69] studied the outcomes of antidepressant trials for 41 patients with bipolar depression and 37 with unipolar depression matched by age and sex distribution. They found short-term nonresponse was more frequent in bipolar (51.3%) than unipolar (31.6%) depression. Furthermore Forty et al. [70] compared some clinical features of depression including course of recurrences in a large sample of in a large sample of individuals with major depressive disorder (N=593) and bipolar disorder (N=443). They

found the number of depressive episodes was higher in patients with bipolar depression (*P*=0.006).

Considering the controversial results of the previously performed studies in how much of variability in response to treatment and its outcome might be related to other clinical characteristics of patients or how these factors might affect the metabolizing capacity of antipsychotic drugs, further investigation is required to delineate the relative importance of these confounded variables when predicting the response to treatment of depression.

Our results were drawn from a relatively small set of patients included in a retrospective case-control study and consequently should be interpreted with consideration for the limitations of the study and its design. The major issue for this study and similar ones is the sample size. The frequencies of UMs and PMs might be altogether 10-20% of population. Our study was powered to capture a potential medium effect size of 0.2 in at least one of the *CYP2D6* phenotypes (N=282, df=3, effect size=0.2 at α=0.05 and β=0.20); however, it is probable that the effect size of the association of *CYP2D6* phenotypes of poor and ultrarapid metabolizers is small and less than 0.2. Accordingly, a large sample size (N≈1000 for df=2 or 3, effect size of 0.1 at α=0.05 and β=0.20) is required to capture substantial number of these *CYP2D6* phenotypes and their effect size of interest for clinical studies. In addition, most patients had undergone repeated treatment trials with different medications, which might have caused a heterogeneous sample. This will cause more loss of power for such clinical trials with relatively small to medium sample size.

The unipolar and bipolar depressive patients in our study groups (ECT cases and patients with single episode of depression) represent extreme clinical outcomes (phenotypes) of depression regardless of type of depression; i.e. one group who had received several prior treatments and eventually indicated for ECT and the other with only a single episode of depression. It has been recommended that distinction between unipolar and bipolar depression would help in initial and optimal management. [70, 71] However, according to some biological evidences, it has been suggested that it might be more useful to consider conceptualizing bipolar and unipolar depression as the same illness with the presentation of its clinical features in continuum, particularly when it applies to depressive episodes. [30, 72]

In conclusion, no increase in prevalence of genotype-predicted-phenotypes was observed among patients who received ECT for continuation of depression treatment as compared to patients with single episode of depression. Therefore, preemptive genotyping for *CYP2D6* currently appears to have no clinical implications in depressed patients undergoing ECT. Further large-scale prospective clinical trials are warranted.

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7

Profound Hypotension during Induction of General Anesthesia with Propofol in Patients with Rifampin Treatment

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Anesth Analg. 2013 Jul;117(1):61-4.

ABSTRACT

Rifampin is commonly used in the treatment of tuberculosis and staphylococcal infections, as well as for prevention of infection in cardiac valve and bone surgeries. We report a case of profound hypotension after anesthesia induction with propofol in a patient who was treated with two 600 mg doses of rifampin for prohylaxis of infection prior to surgery. In a retrospective case-control study of 75 patients we confirmed this potentially serious drug-drug interaction, showing a significant and prolonged blood pressure reduction after anesthesia induction in patients receiving the two agents.

INTRODUCTION

Rifampin is a synthetic derivative of rifamycin B that inhibits bacterial RNA polymerase by forming a stable drug-enzyme complex. [1] It remains one of the most effective antimicrobials used in the treatment of tuberculosis [2], but it is also used to treat methicillin-resistant as well as methicillin-sensitive staphylococcal infections [3], or for prevention of infection in cardiac valve and bone surgeries. [4-6] Here, we report a case of profound hypotension after anesthesia induction with propofol in a patient who was treated with rifampin. We examined for this potentially important drug interaction with a retrospective case-control study of 75 patients.

Case Report

A 64 year old female (weight 88 kg, height 163 cm and BMI=33) presented to our institution for an elective posterior decompression of a herniated disk at the L5-S1 level. She had a past medical history significant for lumbar stenosis, symptomatic gastro-esophageal reflux disease, hyperlipidemia, osteoporosis, and panic attacks. Her medications were atorvastatin (10 mg/day), esomeprazole (40 mg/day), and naproxen (1000 mg/day). She also took acetaminophen plus hydrocodone (5-325 mg) as needed for pain, and occasional multivitamins. The neurosurgical team prescribed rifampin 600 mg p.o. to be given the night before and 2 hours prior to surgery as prophylaxis for infection. The patient had no known allergies and described herself as physically active. She had a stress test performed three years previously which showed normal exercise tolerance and no evidence of myocardial ischemia. The patient remained NPO for 7 hours after midnight, but she had normal intake of food and fluids before that. She was anxious and the pre-induction heart rate was 102 beats/minute, and BP was 150/90 mmHg. She received 2 mg of midazolam and 150 mcg of fentanyl (1.88 mcg/kg), intravenously. This moderately large premedication caused a decrease in anxiety but minimal respiratory and hemodynamic effects. At 7 minutes after fentanyl administration, rapid sequence induction was conducted using 200 mg of propofol (2.3 mg/kg) and 100 mg of succinylcholine (1.1 mg/kg), and a 7.0 mm endotracheal tube was inserted without difficulty. Three minutes after induction of anesthesia and prior to placing the patient in the prone position, her blood pressure decreased to 60/30 mmHg, and heart rate increased to 112 beats/minute. There was no wheezing or difficulty ventilating and no changes in skin color suggestive of an allergic reaction. Rapid intravenous infusion of normal saline was initiated (800 ml/20 min) in addition to phenylephrine continous infusion (10 mcg/min) with incremental bolus doses, as needed. Ten mg of ephedrine (two 5 mg doses) and 80 mcg phenylephrine bolus were administered. Despite continued infusion of fluid, phenylephrine and ephedrine, her sytolic blood pressure remained 60-70 mmHg (> 40 mmHg reduction from baseline), although all central and peripheral pulses were palpable. Epinephrine was added in 0.04 mg bolus doses in addition to 80 mcg

doses of phenylephrine. After administering two doses of epinephrine (0.08 mg) and three more doses of phenylephrine (240 mcg), the patient's blood pressure finally improved to 92/53 mmHg. (figure 1) Serial EKGs showed no signs of ischemia or dysrhythmia during the hypotensive period or afterwards. She remained stable without additional epinephrine, although phenylephrine infusion was required to maintain systolic blood pressure within 70% of her baseline (90-100 mmHg). After some discussion, it was decided to proceed with the surgery with addition of normal saline infusion (1 L/hr) to her continuous phenylephrine infusion. Approximately 35 minutes after induction, the patient was turned prone without hypotension, and surgery was completed without incident. The patient emerged from anesthesia and was extubated without problems. Her postoperative period was uneventful and she was discharged to her home on postoperative day 3 with a satisfactory outcome.

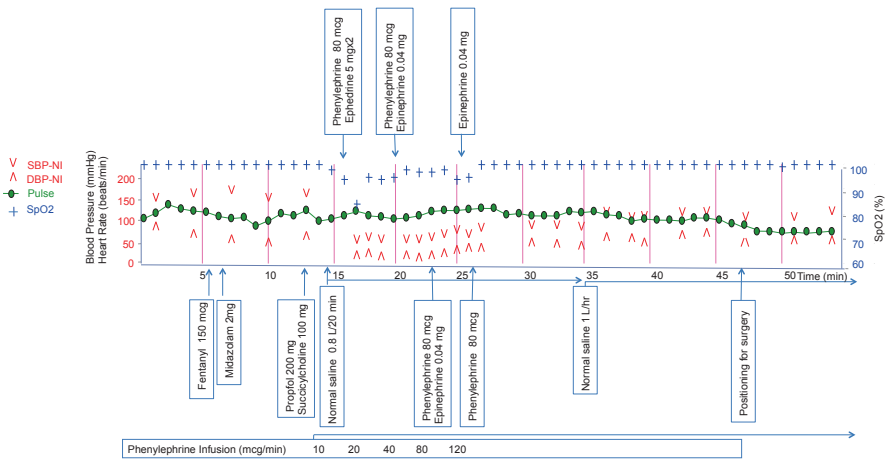

Figure 1. Blood pressure, heart rate and oxygen saturation curves in the reported patient; including administered vasoperessors and fluids in treatment of profound induced hypotension after induction. SBP-NI= systolic blood pressure-noninvasive, DBP-NI=diastolic blood pressure-noninvasive

Retrospective data

Rifampin is not frequently administered for infection prophylaxis, but it had been used this way for several years by members of our neurosurgical division (MGH) doing spinal surgery. There had been anecdotal descriptions of similar hypotensive episodes by the neuroanesthesiologists in our department, and a connection with rifampin had been raised as a possibility. After the present dramatic episode occurred, we felt it was important to investigate our anesthesia and medical record database with the aim of identifying a potential new drug-drug interaction.

After institutional review board approval, we reviewed 194 anesthesia records and medical charts of patients who had undergone spine surgery under general anesthesia between 2008 and 2010 in our institution. We randomly selected 25 patients for each of three groups that were matched for type of surgery and surgeon:

1. Patients receiving propofol for induction of anesthesia and preoperative rifampin prophylaxis, (experimental group).

2. Patients receiving propofol for induction but no rifampin pre-treatment (propofol control).

3. Patients receiving thiopental for induction and preoperative rifampin (thiopental control).

Our prospective power analysis indicated that group sizes of 25 would have 90% power to detect a 10 mmHg difference in MAP reduction at a significance level of 0.05 (two-sided comparison), assuming a standard deviation of 10 mmHg. [7, 8] The prophylactic dose of rifampin was uniformly 600 mg p.o., the night before and on the morning of surgery (usually about 2 hours before) in both the propofol and thiopental groups. Patient characteristics (sex, age, height, weight, ASA physical status classification, Charlson Comorbidity Index (CCI), [9] first and total dose of intravenous anesthetics, total doses of vasopressors, fentanyl dose and volume of administered fluids were recorded. Baseline (time of induction) and post-induction values of systolic, diastolic and mean blood pressure were obtained from the electronic anesthesia record system.

Differences between the groups in sex, age, weight, ASA, and CCI were examined by ANOVA for continuous variables and Kruskal–Wallis ANOVA for quantal variables. Mean blood pressure responses were compared by two-way ANOVA for repeated measures. Our dependent variable, change in MAP, was normally distributed for the three groups as assessed by the Shapiro-Wilk test. There was homogeneity of variance between groups as assessed by Levene's test for equality of error variances. The change in MAP with time was analyzed for each of the study groups using a general linear univariate model to account for the impact of age, type and dose of anesthetic agent, fentanyl dose prior to induction, ASA status, CCI, presence of diabetes and hypertension, weight, location of surgery (cervical vs. lumbar), vasopressor doses and amount of fluid administered.

The significant covariates (duration of hypotension, fluid amount, anesthetic agent, presence or absence of rifampin) were examined in a general linear multivariate model. In the multivariate analysis, anesthetic agent was an independent predictor of hypotension ($p<0.001$).

The induction dose of propofol did not differ between the groups. Patients' baseline characteristics (Table 1) did not significantly influence nadir MAP. We did not find any association between preexisting hypertension and hypotensive events using chi square and binary logistic regression (p=0.564). Patients receiving rifampin and propofol had a significantly greater reduction in their MAP and duration of hypotension than propofol alone or thiopental with rifampin (Table 2) despite the fact that they received lower doses of fentanyl for induction (250 ± 65 mcg) (Table 1). A post hoc test (Tukey's Honestly Significant Difference [HSD]) also showed a significant difference in nadir MAP (p=0.004) and reduction of MAP (p<0.001) in patients with rifampin and propofol vs. propofol alone or thiopental-rifampin. The dose of phenylephrine was not normally distributed, and the Kruskal-Wallis ANOVA showed a significantly greater dose of phenylephrine in the propofol-rifampin group vs. our control groups (p=0.039, Table 2).

Table 1. Demographics and baseline clinical characteristics of the study groups

	Propofol-rifampin N=25	Propofol N=25	Thiopental-rifampin N=25
Age (years)	57 (15)[a]	60 (17)	59 (11)
Sex (F:M)	15:10	12:13	13:12
Weight (kg)	78 (19)	74 (18)	82 (22)
Range	51-120	43-103	49-135
ASA			
Median	2	2	2
Range	1-3	2-3	1-3
Comorbidity Index			
Median	1	2	1
Range	0-4	0-15	0-16
Diabetes Mellitus (no.)	5	6	3
Hypertension (no.)	11	14	9
Baseline MAP (mmHg)			
Mean	100 (14)	94 (14)	93 (12)
Range	75-127	70-123	72-111
Induction dose (mg)			
Mean	176 (74)	183 (69)	396 (129)
Range	100-350	110-400	150-600
Fentanyl induction dose (mcg)			
Mean	250 (65)	325 (199)	220 (59)
Range	150-450	150-750	50-250

[a]Standard deviation (SD), unless otherwise indicated

Table 2. Hemodynamic responses and vasopressor treatments during induction

Group	MAP Nadir Mean (SD) mmHg	MAP Nadir Mean (SD) mmHg	Time to Nadir MAP min	Hypotension Duration Mean (SD)[b] min	Phenylephrine Median [Range] mg	Ephedrine Median [Range] mg	Fluid (SD) RL/NS[c] Mean (SD) mL	Odds ratio[d] (95 % CI)
Propofol-rifampin	58 (13)*	-38 (3)**	13 (11)**	33 (13)***	17 [0-77]****	0 [0-50]	1950 (753)***	11 (3-39)***
Propofol	71 (15)	-22 (2)	6 (5)	13 (8)	7 [0-16]	0 [0-50]	1320 (593)	4 (1-13)
Thiopental-rifampin	76 (11)	-16 (3)	5 (4)	9 (5)	2 [0-10]	0 [0-35]	1290 (394)	0.36 (0-10)

*p<0.004 vs. propofol alone or thiopental-rifampin
**p<0.001 vs. propofol alone or thiopental-rifampin
***p<0.005 vs. propofol alone or thiopental-rifampin
****p =0.039 vs. propofol alone or thiopental-rifampin

[b] Duration of hypotension was defined as time of reduction of mean blood pressure (MAP) after induction to nadir and its return to 90 % of pre-induction (baseline) value. [c] RL (Ringer's lactate), NS (normal saline), [d] Hypotension was defined as occurrence of SBP<90 mmHg or more than 40 % change from baseline SBP. Odds of occurrence of hypotension were calculated in each group and adjusted for the covariates. Change from baseline values of mean arterial pressure (delta MAP).

DISCUSSION

This case report and the retrospective data analysis demonstrated that the risk of a prolonged hypotensive episode increased almost three-fold when propofol rather than thiopental was used for induction in patients who received rifampin. In 10 of 25 cases, this exaggerated hemodynamic response required vigorous treatment with vasopressors and fluids, i.e., hypotension persisted despite more than 2 L Ringer's lactate (or normal saline) as well as repeated doses of vasopressors. The peak hypotension might actually have been underestimated, since these patients did not have continuous measurements with an arterial line.

In our retrospective data analysis the duration of fluid abstinence did not differ between the groups [10], nor did the dose or type of pre-induction anxiolytic agent (midazolam). The induction dose of propofol was similar with or without rifampin, and the fentanyl dose was lower in the propofol-rifampin group. However, the hemodynamic response was significantly greater in the propofol-rifampin group, suggesting a drug-drug interaction as the cause. Hemodynamic instability was not seen when rifampin was given with thiopental, indicating that the interaction is unique to propofol.

The mechanism for this interaction was not investigated. Intravenous administration of rifampin alone can induce hypotension by a direct, dose-dependent reduction of vascular tone and SVR, [11] and propofol-induced hypotension is largely due to venodilation. [12] However, it is not clear if oral administration of rifampin will do the same and whether any such effect would be relevant for propofol administration so many hours after the first and second doses.

Anaphylactic or anaphylactoid reactions caused by the induction agent [13-15], or rifampin [16] are unlikely, given the lack of hypotension in the control groups. In no case, did the clinicians record urticaria or flushing, bronchospasm, or mucosal edema. One mechanism that is suggested to promote hypotension after propofol administration is related to its direct effect on venous smooth muscle tone, presumabley through increased endothelial production and release of nitric oxide (NO). [17] Rifampin might augment this effect as a result of increased NO production by upregulating iNOS mRNA transcription.[18] This increase in NO levels has only been demonstrated *in vitro*, but it does occur within 20 hours after exposure to clinically relevant concentrations of rifampin (10 to 100 µg/ml). The serum concentration of rifampin after 2 hours following a single 600-mg oral dose was reported to be 8.8-12 mcg/ml [19-21] and in another study 15.9 mcg/ml (4), so the NO mechanism is a plausible explanation with the antibiotic concentrations likely present in our case. The serum concentrations of rifampin in the latter study dropped from 15.9 ± 6.5 mcg/ml at 2 hr, to 7.1 ± 4.3 at 8 hr, with 1.6 ± 1.6

mcg/ml still detectable at 24 h. (4) This suggests that sufficient rifampin may be present to cause drug-drug interactions for a significant period of time after typical oral dosing.

Rifampin is commonly used for treatment of tuberculosis and less often for prophylaxis of staphylococcal infections and nisseria meningitidis infections. It is rarely used for routine preoperative antimicrobial prophylaxis, which could explain why this interaction with propofol may not have been appreciated previously. Clinicians should be aware of this potentially dangerous interaction and if rifampin is necessary, consider using alternative agents for induction of anesthesia. A prospective study is desirable to investigate the mechanism of this drug-drug interaction.

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8

Severe postoperative hemodynamic events after spinal anesthesia a prospective observational study

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Journal of Anesthesiology and Clinical Science 2012,1:14.

ABSTRACT

Background

Postoperative hemodynamic adverse severe events (PHASE, severe bradycardia and hypotension) can occur during recovery from spinal anesthesia. The incidence, contributing factors and consequences of PHASE are not well described.

Methods

232 consecutive patients were included in this prospective observational study. PHASE was defined as a combination of heart rate <45 bpm, and systolic blood pressure <70 mmHg. Correlation analysis was used to identify potential predictors of PHASE and then a multivariate logistic regression model was constructed to evaluate independent predictors of PHASE. PACU lengths of stay between patients with and without PHASE were compared.

Results

Fifteen patients presented with severe hypotension (SBP 64.5±10.6 mmHg) and twelve patients with severe bradycardia (heart rate of 40±5 bpm), resulting in PHASE in 10 patients. PHASE occurred on average 307±82 min after spinal anesthesia with a mean spinal anesthesia level of L1 at the time of PHASE. Insertion of spinal anesthesia in the lateral position (PHASE: 80%, no PHASE: 34%, p=0.030) and morphine dose (20±12mg versus 9±8 mg, respectively p=0.011) were found to be independently associated with PHASE. PHASE was associated with a 60-minute increase in median PACU length of stay.

Conclusion

PHASE occurs in about 5% of patients recovering from spinal anesthesia. The average time for PHASE onset is 307±82 min. The events are associated with insertion of spinal anesthesia in the lateral compared with sitting position, and with postoperative opioid administration. PHASE during recovery from spinal anesthesia is associated with significantly increased PACU length of stay.

BACKGROUND

Hypotension and bradycardia are the most common complications associated with spinal anesthesia[1, 2], occurring in the intra-operative period due to decreases in systemic vascular resistance and central venous pressure from sympathetic block.[1] Postoperatively, cases of spinal anesthesia associated severe bradycardia have been described to occur up to 5 hours after arrival in the Post Anaesthesia Care Unit (PACU).[3] To the best of our knowledge, there has been limited description of the epidemiology of severe bradycardia and hypotension during the recovery from spinal anesthesia. The primary study objectives were to determine whether PHASE is associated with increased PACU length of stay.

METHODS

The study was approved by Partners Health Care Institutional Review Board, and conducted in the 32-bed PACU of the Massachusetts General Hospital (MGH) in Boston, Massachusetts, a teaching hospital that serves as a tertiary care referral center, level-1 trauma center, and community hospital for the inner city population of Boston. The PACU staffing model consists of an anesthesia resident on site 24 hours a day, a supervising staff intensivist, a respiratory therapist and a nurse-staffing ratio of 1 nurse for every two patients.

Subjects

We included 232 consecutive ASA physical status 1-3 patients undergoing orthopedic lower limb surgeries arriving in the PACU after spinal anesthesia. Patients with incomplete data sets were excluded from the study and 190 patients with complete data set were included in data analysis (Table -1).

PHASE: A focus group of experienced anesthesiologists and PACU nurses was held to develop a definition of severe postoperative hemodynamic events occurring after spinal anesthesia. Based on the results of this focus group, PHASE was defined as combination of heart rate < 45 bpm, and systolic blood pressure <70 mmHg.

Protocol

Patients were given either 1-2 mg intravenous midazolam as a premedication up to 1 hour prior to spinal placement. Patient care was delivered in the usual manner and was not altered in any way by the investigator. Board certified staff anesthesiologists supervised all anesthetics. In accord with departmental guidelines, all patients were preloaded with 500-1000 ml of ringers lactate prior to spinal anesthesia, which was followed by slow infusion of ringers lactate. Hyperbaric bupivacaine 0.5%, 3.6±1ml (mean and standard deviation) was

Table 1: Patient Demographics

	No hemodynamic event N=173(91%)	Hypotension N=15 (7.9%)	Bradycardia N=12(6.3%)	PHASE N=10(5.2%)
Gender (male)	49%	47%	42%	40%
Age (years)	67±11	66±8	67 ±7	67±4
Height (inches)	66±7	67±3	68±4	66±4
Weight (kg)	85±24	80±12	82±11	80±12
ASA* 1	8			
ASA 2	133	1	1	
ASA 3	32	14	11	10
Cardiovascular risk factors	65%	56%	50%	62%
Beta-blocker taken in the morning	32%	6.7%	8.3%	10%
Other anti-hypertensives taken in the morning	39%	33%	25%	30%

*ASA physical status classification system

injected into L2-3 or L3-4 interspace with the patient in either sitting or lateral position. Standard anesthesia monitoring (electrocardiogram, heart rate, pulse oximetry and oscillometric blood pressure) was used continuously throughout the OR portion of care. Immediately after spinal placement, patients were positioned horizontally and supine as described in the Clincial Prcedures of the Masschusetts General Hospital. [4] Side effects of spinal anesthesia such as nausea and vomiting were documented and treated. Patients with blood loss of more than 20% of blood volume were treated with colloids and RBC transfusions. After surgery, patients were transferred to the PACU in the supine position with the head of the bed elevated by 20-30 degrees. Intravenous morphine or hydromorphone were used to provide postoperative analgesia.

Measurements

Preoperative data collected for patients enrolled in the study were age, weight, height, gender and history of medical illness (diabetes mellitus, hypertension, stroke, arrhythmia, previous myocardial infarction) and medications use (angiotensin converting enzyme inhibitors, adrenergic blockers, calcium antagonists, and diuretics).

Intraoperative data collected on study patients included blood pressure and heart rate, temperature, respiratory rate and oxygen saturation. Severe hypotension was defined as systolic blood pressure less than 70 mmHg that required treatment with a vasopressor. Severe bradycardia was defined as heart rate <45 beats per minute that required treatment with ephedrine or atropine. Total duration of surgery was also recorded.

On the admission to the PACU, PACU nurses who were not involved in the study documented the following data: skin temperature (forehead non-contact infrared thermometry), blood pressure, peripheral oxygen saturation, and spread of spinal anesthesia (dermatomal level, determined by pin prick). Standard PACU monitoring was then conducted according to institutional protocol (blood pressure, heart rate, five-channel EKG, peripheral oxygen saturation, Aldrete score). Following admission to the PACU dermatomal level of anesthesia was recorded in 15 minutes intervals until full recovery from spinal anesthesia. All patients were closely monitored in the PACU for the occurrence of PHASE which was documented in the patient's chart and was treated by the PACU attending physician and/or resident, as appropriate. The decision about PACU readiness was made by the PACU nurse and the PACU resident. According to Departmental guidelines, patients were considered ready for discharge after adequate pain control was achieved, they were cardiopulmonary stable, and their sensory residual spinal anesthesia level was below S1. PACU length of stay was defined as the time from PACU admission until PACU discharge readiness. PACU length of stay was recorded by the PACU charge nurse not involved in this study.

Statistical Analyses

Sample size estimation for the study was based on the study hypothesis that PHASE prolongs the PACU length of stay. We used the reports of Ponhold[3] and Butterly [5] to calculate the required sample size. Based on the report of Ponhold[3], describing post operative bradycardia , we expected a PHASE incidence of five to ten percent. We recently reported on the association of postoperative complications and PACU length of stay. [5] Based on these data, we estimated that PHASE might be associated with a 60-minute difference in PACU length of stay with a standard deviation of 60 minutes. Accordingly, we expected that a sample size of 190 patients would provide a 90% power to detect an effect of PHASE on PACU length of stay (alpha-error: 5 per cent).

Data analysis was performed using the statistics program SPSS (V 12.0, SPSS Inc., Chicago, Ill). Demographic data are presented as mean ± standard deviation for continuous variables and as frequencies and percentages for discrete variables. The dichotomous variable PHASE defined as a combination of heart rate <45 bpm, and arterial blood pressure <70 mmHg, was used as the primary endpoint. The Mann-Whitney U test was used to compare the PACU length of stay in patients with and without PHASE.

The study objectives were to: determine whether PHASE is associated with increased PACU length of stay. Before start of the study we performed a comprehensive literature review. We also held focus group with experienced anesthesiologists and PACU nurses to discuss potential causes of PHASE. A priori, we identified three categories of variables potentially

associated with PHASE: 1) patient associated factors including basic demographics, comorbidities, and ASA physical status 2) intraoperative factors, 3) effects of treatment in the PACU.

Chi square analysis was used to examine the association between PHASE and categorical variables while the t and Mann-Whitney U tests were used to compare normally and non-normally distributed continuous variables respectively between the PHASE and non-PHASE groups. Variables that we considered a-priori to be potential preoperative, intraoperative and postoperative predictors of PHASE included: gender, age, height, weight, preoperative heart rate, preoperative systolic blood pressure, preoperative diastolic blood pressure, preoperative EKG abnormality, preoperative conduction disorder, preoperative use of beta blocker, use of other antihypertensives, patient in lateral position during spinal bupivacaine injection, bupivacaine dose, negative fluid balance, use of vasopressors in OR, use of ephedrine in OR, use of intravenous opioids in OR, episode of bradycardia in OR, PACU heart rate, PACU blood pressure systolic, thoracic level of spinal anesthesia at PACU admission, use of IV narcotics in PACU, long-acting opioid dose (morphine equivalents – assumption: one milligram of hydromorphone is equal to 6 mg of morphine), and IV administration of antiemetics in the PACU.

Backward stepwise multiple regression analysis was then used to investigate independent factors with a significant association to PHASE within a multivariate model. Variables with the strongest significant contribution ($p < 0.05$) were regarded as the independent factors associated with the primary endpoint.

RESULTS

Univariate analysis

Intraoperative course

Initial blood pressure was significantly higher in patients with severe hypotension when compared to patients with no events (table 2). A significantly higher proportion of PHASE patients compared with patients without hemodynamic events (80% versus 20%, $p<0.05$) received spinal anesthesia in lateral position. There was no significant difference in terms of dose of bupivacaine used in spinal anesthesia and relation between the occurrence of intraoperative bradycardia and hypotension with that of severe bradycardia and hypotension postoperatively.

Postoperative course

Variables measured in the PACU are presented in Table 3.

Table 2. Intraoperative data

	No hemodynamic event N=173(91%)	Hypotension N=15 (7.9%)	Bradycardia N=12(6.3%)	PHASE N=10(5.2%)
Heart rate prior to induction (bpm)	74±11	71±11	66±11*	69±13
Systolic blood pressure prior to induction (mmHg)	137±19	130± 21	144± 9	149±16*
Diastolic blood pressure prior to induction (mmHg)	75±123	73±11	75±10	76±11
Position during spinal bupivacaine administration	LATERAL-34% SITTING-66%	LATERAL-57% SITTING-43%	LATERAL-67%* SITTTNG-33%	LATERAL-80%* SITTNG-20%
Bupivacaine dose (mg)	17.5±4.5mg	18 ±1.5mg	18.5± 2.5mg	18.5±1.5mg
Intraoperative vasopressor	73%	67%	50%	50%
Intraoperative bradycardia	0	0	8.3%	0
Intraoperative antiemetics	37%	46%	25%	30%
Intraoperative opioids	73%	80%	83%	80%

* P<0.05 vs. patients without PHASE

Table 3: Measurements taken in PACU

	No hemodynamic event N=173(91%)	Hypotension N=15 (7.9%)	Bradycardia N=12(6.3%)	PHASE N=10(5.2%)
HR at admission	68±13	65±12	60±10*	62±9.6
Systolic blood pressure at admission	119±18	100±26*	110±31	103±29*
Cranial spread of spinal anesthesia at PACU admission	<T12:72 (48%) >L1:47 (22%)	>T12:7 (47-%) >L1:8 (53%)	<T12: 5 (42%) >L1: 7 (58%)	<T12: 5 (50%) >L1: 5 (50%)
IV Narcotics in PACU	80%	87%	100%	100%
Morphine equivalent dose (mg)	9±8 mg	18±12 mg*	19±12 mg*	20±12mg*
PACU length of stay	210±108	360± 270*	312±312*	350±318*
Time from spinal placement to event		304±94.	300±79	307±82
Heart rate (during event)		50.22±18.55	40±5	41±5
Systolic blood pressure during event		64.5±10.6	69.31±16.27	62±8
Cranial spread at time of event		<T12-4 (27%) >L1-5 (33%) L5-S4: 6 (40%)	<T12-4 (33%) >L1-4 (33%) L5-S4: 4 (33%)	<T12-3—30% >L1-4 (40%) L5-S4: 3 (30%)

* P<0.05 vs. patients with no events.

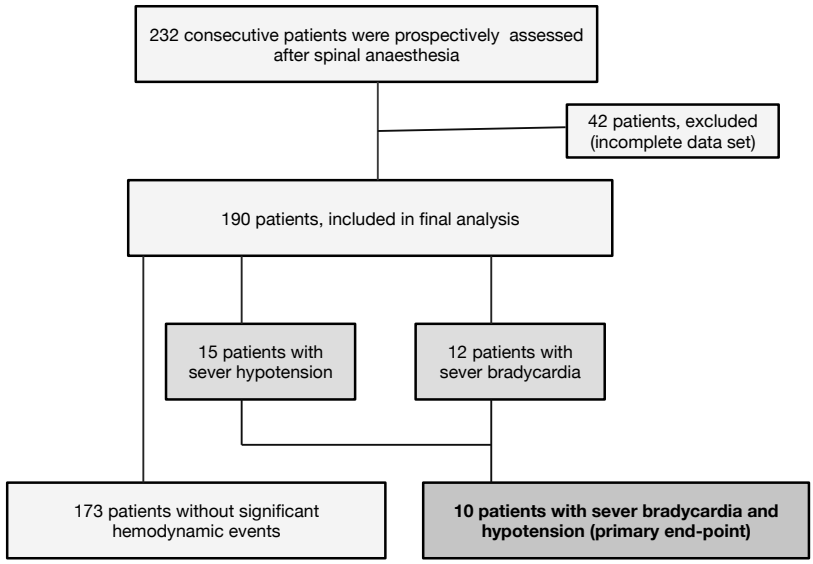
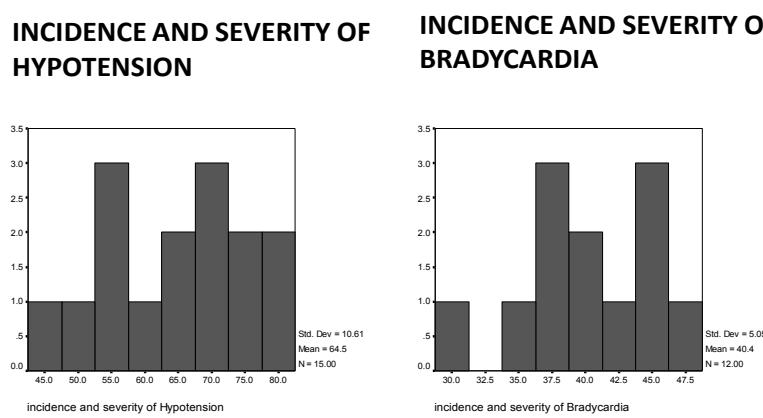


Figure 1. Consort flow diagram

A.



- N=15 (7.9% of patients with SpA)
- MEAN SYS BP--64.5±10.6
- N=12 (6.3% of patients with SpA)
- MEAN HEART RATE--40±5

Figure 2. A and B. Incidences and severity of PHASE components

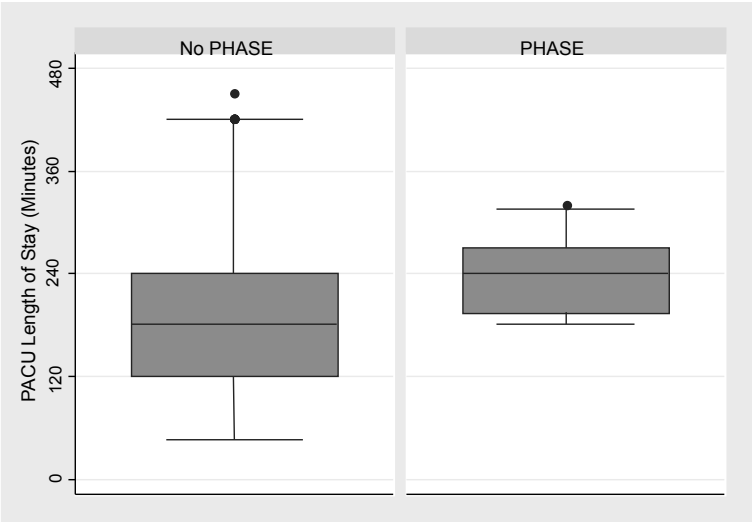


Figure 3. Effects of severe PHASE on PACU length of stay

During the observation period in the PACU, all patients had oxygen saturation >95% without oxygen mask. Fifteen patients presented with severe hypotension (SBP 64.5±10.6 mmHg) and twelve patients with severe bradycardia (heart rate of 40±5 bpm) (figure 2A). Ten patients presented with PHASE, both severe hypotension and bradycardia in the PACU, the main endpoint of our study. Accordingly, the incidence of severe adverse hemodynamic events was 5.2%. Mean time to occurrence of PHASE was 307±82 min. Median residual level of spinal anesthesia at PACU admission was L1, without differences between patients with and without PHASE.

In the univariate analysis, the following variables were associated with PHASE: Thoracic level of spinal anesthesia at PACU admission (p<0.0001), morphine equivalent dose (p=0.006), total intraoperative fluids (p=0.031), preoperative heart rate (p=0.046), intraoperative vasopressor treatment (p=0.015), and lateral versus sitting position (p=0.038).

Multivariate analysis

To identify independent predictors of PHASE, a backward stepwise regression analysis was performed, which initially included the variable found to be associated with PHASE in the univariate analysis*:* position during insertion of spinal anesthesia (sitting versus lateral flat), preoperative heart rate, intraoperative vasopressors treatment, as well as opioid dose used in PACU. Insertion of spinal anesthesia in the lateral position (event group: 80%, no-event group: 34%, p=0.030) as well as morphine dose (20±12mg versus 9±8 mg, respectively p=0.011) were found to be independently associated with a severe, adverse hemodynamic

event. None of the patients who developed PHASE required cardiopulmonary resuscitation; however all were treated with either atropine, and/or ephedrine.

Effects of severe PHASE on PACU length of stay

PACU length of stay was significantly longer in patients with adverse severe hemodynamic events (median 240 min, IQR 75 min) compared with patients with no adverse hemodynamic events (180 min, IQR 120, p=0.233;figure 3).

DISCUSSION

PHASE occurred in 5% of the patients recovering from spinal anesthesia and was associated with a prolonged PACU length of stay. The combination of bradycardia and hypotension causing hemodynamic instability make PHASE a potential life-threatening event. Identifying factors associated with PHASE might help to decrease the incidence.

In our study, the patient's position during spinal placement, as well as the postoperative opioid dose, were independent predictors of PHASE.

Factors contributing to development of hypotension *early* after spinal anesthesia placement have been well documented. [6,7] Acute hemodynamic effects of spinal anesthesia may be explained by sympatholysis, resulting in three major hemodynamic effects: decrease in venous return (in turn influenced by posture, bleeding and inferior vena cava compression), vasodilatation and decreased cardiac output.[8]

Bradycardia regularly occurs in patients with higher levels of sympathetic block involving the cardiac accelerator fibers (T1-T4), but this effect was most likely not relevant in our patients. In our patients, the median cranial margin for blockade was L1 and it was substantially lower by the time PHASE occurred (lower lumbar level in 70% of our PHASE patients). Therefore, even though the uppermost level of spinal anesthesia measured by temperature elevation is up to 6 levels higher compared to the upper limit of sensory blockade [9], it is unlikely that ongoing blockade of cardiac accelerator fibers that can explain the findings of PHASE occurring many hours after placement of spinal anesthesia.

We speculate that vagal over-activity, potentially due to a combination of visceral stimulation and opioid effects might have been contributing. Since abdominal visceral structures, such as peritoneum, are innervated by fibers from both limbs of the autonomic nervous system, blockade of sympathetic nervous system supply to these organs may result in unopposed parasympathetic nervous system activity. When visceral stimulation, e.g., bladder distension,

or visceral pain takes place under these circumstances, parasympathetic afferent transmission may lead to reflexive vagal efferent effects, unrestrained by sympathetic counterbalancing, resulting in bradycardia. [10]

The magnitude of hypotension and bradycardia occurring early after spinal administration of local anesthetics should depend on the spread of the sensory block height. In our study, the independent predictor was the position in which the spinal anesthesia was inserted, a variable that is clearly related to the spread of anesthesia. When using hyperbaric bupivacaine, which we did in our study, the onset time to analgesia is shorter in the lateral compared with sitting patients, and hypotension occurs more frequently.

Opioid induced bradycardia [11] may also have contributed to PHASE in part via inhibiting the activity of cardiac vagal neurons.[12, 13] Furthermore, pre-operative administration of opioids has been shown to be an independent risk factor for intraoperative hypotension in patients undergoing spinal anesthesia.[14] Therefore, we speculate based on our data that the combination of residual (lumbar) neuraxial block and opioid effects contributed to PHASE in our patients. In our study PHASE was associated with lateral positioning during administration of spinal anesthesia was associated with PHASE. Based on this finding, lateral positioning during placement of spinal anesthesia might be avoided especially in patients with other identified risk factors for PHASE.

The 6.3% incidence of bradycardia found in the PACU during recovery from spinal anesthesia is similar to the incidence reported by Ponhold and co-workers[3] despite slightly different definitions Ponhold defined bradycardia as heart rate lower than 50 bpm, whereas we used a 45 bpm cut-off point, which we believed to be more clinically meaningful.

The time of occurrence of PHASE was similar to the report of Ponhold and Vincenzi. These authors reported the latest occurrence of severe bradycardia 320 min after admission to the PACU. Similarly we observed PHASE 455 min after admission to the PACU. This late occurrence of PHASE makes decisions regarding discharge from the PACU very difficult. The practice guidelines for postoperative care by the American Society of Anesthesiologist's Task Force on Post Anesthetic Care [15] provide little guidance on the best timing for discharge of patient after spinal anesthesia. It states "Patients should be observed until they are no longer at increased risk for cardio-respiratory depression. A *mandatory* minimum stay should not be required. Discharge criteria should be designed to minimize the risk of central nervous system or cardio-respiratory depression after discharge". After spinal anesthesia patients are often discharged from the PACU after recovery for motor and sensory function. The concept of orthostatic stability as discharge criteria was introduced by Alexander et al [16] and later

confirmed by Knoerl et al. [17] These authors reported that using orthostatic blood pressure testing instead of return of motor sensory function could decrease the PACU length of stay to 62 min. While we did not perform orthostatic blood pressure testing it is clinically important that PHASE occurred on average 300 min after placement of spinal anesthesia even in the absence of profound motor block. We conclude based on our data that patients should optimally not be discharged from the PACU until full recovery of sensory and motor function has been documented. Further studies are required to define and test optimal clinical criteria for safe transfer of patients from the PACU.

Severe bradycardia and hypotension can become a life threatening events. None of our patients developed cardiopulmonary arrest; however all required a combination of vasopressors and chronotropic agents. It can be speculated that only the vigilance and early intervention of the PACU staff averted more catastrophic outcomes. Based on the results of this study, our PACU staff now receives periodic refresher training regarding the occurrence and treatment of PHASE in patients' post-spinal anesthesia.

PHASE was associated with a significant increase in PACU length of stay. The magnitude of the effects of PHASE on PACU length of stay is economically meaningful only under the condition that an institution conducts a high volume of spinal anesthesia.

This was a single center study in an academic tertiary care center, which limits the ability to generalize the findings to different settings. The study was designed as a prospective observational study, which limits the ability to control variables of the study. The intraoperative course including spinal anesthetic was not controlled. It is therefore possible that other factors may influence the occurrence of PHASE. Finally the study's sample size and low incidence of PHASE may have limited our ability to identify risk factors for PHASE especially their contribution in the multivariate analysis.

CONCLUSION

In summary, we found that PHASE occurs in 5% of the patients recovering from spinal anesthesia, and is associated with a prolonged PACU length of stay. In our patients, the patient's position during spinal insertion, as well as the postoperative opioid dose, was independent predictors of PHASE. Further studies are required to define and test optimal clinical criteria for safe transfer of patients after spinal anesthesia.

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9

General Discussion and future directions

Electroconvulsive therapy (ECT) is the transcutaneous application of small electrical stimuli to the brain to produce generalized seizure for the treatment of selected psychiatric disorders, typically. ECT owes its current acceptance to modern anesthesia. Indeed, a cornerstone of the periprocedural management of patients receiving ECT is the proper selection and use of anesthetic drugs and techniques tailored to mitigate the associated physiological response and potential complications, without interfering with its beneficial effects. [1] A combination of a short acting induction agent (e.g. propofol), neuromuscular blocking agent (i.e. succinylcholine) and hemodynamic monitoring under supervision of anesthesiologist and in collaboration with psychiatrists has favorably yielded more safety for this short treatment procedure. Furthermore, anesthesia medications applied during ECT could augment the response to induced seizure (e.g. the NMDA receptor antagonist ketamine) as well as increasing the safety of the procedure.

Safety of ECT increases the efficacy of therapy and provides fulfillment of a series of required treatments resulting in longer treatment effect of ECT. Over the decades many efforts have been made to reduce the special risks in ECT. As a result, the safety and efficacy of ECT has been improved and its indications have been relatively defined to increase the efficiency of outcome of therapy.

While there has been considerable improvement in safety features, further investigation have been done to promote both the safety and efficacy of the treatment. These investigations take on greater significance by considering that some aspects of ECT safety (e.g. memory and cognitive effects) could partly be inherent to unknown induced biological mechanisms correlating with transmitters involved in the outcome of treatment (efficacy). However, this correlation is not the same in all patients suggesting a more prominent role of pharmacogenetics in ECT. Neurotransmitters such as dopamine, norepinephrine, and serotonin systems are more involved with depression. These neurotransmitter systems along with multitude of other neurochemicals such as endorphins, enkephalins and prolactin, GABA, glutamate and acetylcholine play role in the behavioral manifestations of other psychiatric illnesses. Yet it is unknown which induced neurobiological system(s) by ECT stimulation might be more involved with impairment of memory than efficacy treatment response.

Accordingly, in this dissertation we investigated several important aspects of safety and efficacy of ECT from looking into the current literature to conducting clinical research studies. We attempted to contribute to the existing literature and clinical principals in application of ECT and understanding of the role of pharmacogenetics in ECT.

Neuromuscular blockers in ECT and optimal seizure activity (safety improves efficacy)

Neuromuscular blocking agents (NMBAs) dramatically revolutionized the practice of anesthesia during procedural treatments, particularly in ECT. Neuromuscular transmission blockade mitigates the tonic-clonic motor activity during ECT sessions and provides an effective mean to reduce the physical and psychological trauma associated with uncontrolled tetanic muscle contractions.

Anesthetic drugs and neuromuscular blocking agents (NMBAs) are administered to ensure patient comfort and safety, but need also be titrated to provide optimal conditions for the induced seizure activity during the treatment, while allowing a rapid recovery upon its completion. [2] As an ideal neuromuscular blocker, what is needed is an agent that is rapidly acting, non-cumulative, independent of renal or hepatic function for its elimination, easily and rapidly reversed and free from side effects. While waiting for new muscle relaxants to be developed, we need to opt for optimization of available NMBAs and improvement of neuromuscular transmission (NMT) monitoring. In order to optimize the dose of NMBAs, important pharmacological characteristics of each agent have to be considered, including its potency, speed of onset, duration of action and the muscle-dependent effects. This optimization takes on greater significance as it has been shown that the quality and duration of the induced seizure by ECT is associated with the efficacy of the procedure. [2]

In *chapter two* of this dissertation we reviewed the current applied neuromuscular blocking agents in ECT. We showed that succinylcholine, due to the short onset time and duration of action is the first choice for ECT procedure, however, all the currently available NMB agents have their own limitations and the quest continues for an ideal drug. There were some points to be considered for the application of succinylcholine. The recommended dose range of succinylcholine during ECT had been reported to be 0.5-1.5 mg/kg that is a relatively large range of dose and no clinical guideline for the application of succinylcholine during ECT was identified. [3-6] Furthermore, there are some clinical indications, which application of succinylcholine could be contraindicated or using an alternative is recommended, e.g. elderly patients with risk of hyperkalemia and long length of stay in hospital. [7] The individual and variability in response to succinylcholine and other NMB agents is also another point of consideration. [8, 9] Owing to these factors, and based on the systematic review conducted in *chapter two,* we conclusively suggested seeking an alternative such as rocuronium to be applied for ECT in patients with absolute or relative contraindication of succinylcholine usage. [10, 11] We also showed that similar to succinylcholine, a wide range of rocuronium doses for ECT, i.e. 0.3-0.6 mg/kg has been administered for ECT and no clinical guideline has been recommended for rocuronium application in ECT. Doses beyond 0.4 $mg.kg^{-1}$, for ECT, have

been used in combination with the reversal agent sugammadex, a selective relaxant-binding agent (currently not available in the USA) that has also been used to reverse profound rocuronium-induced neuromuscular blockade in adult surgical patients.[3] Rocuronium and succinylcholine had satisfactorily been compared for other clinical indications such as rapid-sequence induction of anesthesia and the required dose, onset times and clinical duration of actions had been defined. [12, 13]

In pursuit of our suggestion, we designed a randomized crossover clinical trial (*chapter three*) and investigated the optimal doses of succinylcholine and rocuronium for ECT and compare their clinical significance. Consistent with the report from Murali and his colleagues [14], our acquired data suggest that succinylcholine doses closer to one $mg.kg^{-1}$ may provide acceptable ECT conditions and also highlight the importance to avoid early application of ECT after the administration of succinylcholine, i.e. less than 1.4 min even in the absence of a twitch response to nerve stimulation. The 1 $mg.kg^{-1}$ dose is the 90^{th} percentile of optimal effective dose equal to 3.5 × ED_{95} of succinylcholine. Furthermore, in our study an induced twitch height suppression of almost null (0-4%) for acceptable motor seizure modification are in line with findings by Murali and his colleagues, who recommended a dose of 1.0 $mg.kg^{-1}$ and twitch suppression to 0-5% of baseline.[14] This dose has also been applied for rapid sequence intubation (1 $mg.kg^{-1}$of succinylcholine, 3.5 × ED_{95}). [15-17] However our study suggests longer time to achieve adequate muscle relaxation for ECT is required (60 sec for rapid sequence intubation). This observation is also consistent with previous finding by Beale and colleagues [18] that the muscle response to ulnar nerve stimulation can be extinguished long before cessation of muscle fasciculation. This difference in time to obtain acceptable ECT conditions as compared to that for endotracheal intubation may be attributed to a difference in sensitivity to succinylcholine in different muscle groups (e.g. oropharynx versus extremities), but can also indicate that a deeper neuromuscular blockade is needed for acceptable ECT conditions as compared to endotracheal intubation.

Rocuronium 0.57 $mg.kg^{-1}$ (≈ 2 × ED_{95}) was the 90^{th} percentile estimated dose to produce acceptable level of muscle relaxation. This dose has already shown its efficacy in inducing more than > 95% block in almost 98% of subjects.[19, 20] The onset time from NMBA injection to acceptable ECT conditions is hence approximately 2.3 minutes longer with rocuronium as compared to succinylcholine. While we did not identify any difference in major clinical characteristics during seizures such as hemodynamic variables or oxygen saturation between rocuronium and succinylcholine, the recovery time of recuronium was substantially longer than succinylcholine (8 min). However, rocuronium application showed some other qualities not observed by succinylcholine. Consistent with other studies seizure duration was longer in patients who received rocuronium as NMB agent. [21] As there is an association

between clinical effectiveness of ECT and the duration of induced seizure [22], the American Psychiatric Association task force advocates seizure lengths more than 20 sec for effective ECT treatment.[23] This recommendation not only underscores the importance of titrating the dose of the NMBA to achieve an adequate and optimized neuromuscular blockade, but also this quality might be of interest for potential role in the efficacy of ECT in set of treatments (i.e. cumulative seizure time). Further clinical investigation is warranted.

In *chapter three,* we defined the optimal doses of rocuronium and succinylcholine and demonstrated that even in absence of this selective reversal agent, in patients with contraindications to the use of succinylcholine, [2] the rocuronium-neostigmine combination can provide a safe and relatively time-effective alternative to other available non-depolarizing NMBAs and reversal agents. Rocuronium is increasingly employed as an alternative to succinylcholine for neuromuscular blockade during ECT, primarily in the elderly and patients with cardiovascular and neurological comorbidities. On the other hand, ECT is highly effective and is increasingly applied in the elderly and those with increased incidence of prolonged immobilization, prone to higher risk of hyperkalemia. [3] Nondepolarizing NMBAs do not cause hyperkalemia and can be given to these patients and those with susceptibility to malignant hyperthermia or contraindications to succinylcholine, but are often avoided because of their relatively long duration of action, typically exceeding the ECT time. Our study demonstrated that even in absence of selective reversal agents such as sugammadex, in patients with contraindications to the use of succinylcholine, [2] the rocuronium-neostigmine combination can provide a safe and relatively time-effective alternative to other available non-depolarizing NMBAs and reversal agents.

As compared to rocuronium, succinylcholine showed relatively higher inter-individual variability for the applied effective doses that resulted in acceptable neuromuscular blockade and controlled ECT induced seizure. This fact reemphasized the role of pharmacogenetics in ECT (discussed more in *chapter five*) and how the variability in expression and activity of butyrylcholinesterase enzyme resulting in different observed degradation quality of succinylcholine might have caused this observation. The lower variability in the applied rocuronium doses to identify individualized optimal dose might take on greater significance if achieving the optimized induced motor activity is required to rapidly maximize the therapeutic effect of sequential ECTs, particularly if alternative for succinylcholine is advisable. However after initial dose, if increments are required, less predictable and longer recovery time than increment of succinylcholine doses should be considered. [24, 25]

In general, complete paralysis is neither necessary nor desirable since it may be associated with prolonged apnea. As previously mentioned, currently, no guideline has been described for application of rocuronium during ECT and according to the guidelines of the Nederlandse Vereniging voor Psychiatrie (Richtlijnen Nederlandse Vereniging voor Psychiatrie, tweede, herziene versie, 2010), succinlycholine 0.5-1 mg/kg is recommended for ECT. This ECT guideline also suggests measurement of serum potassium in certain patients i.e. age>60 or use of diuretics, digoxin, corticosteroids, laxatives, antihypertensive drugs, decrease renal function, hypertension and diabetes, as increased potassium levels are a contra-indication for ECT. The guideline does however does not recommend any alternative to succinylcholine, if needed.

In *chapter three*, we tried to provide some clinical suggestions for clinicians for how to apply these two NMB agents. According to our experimental randomized crossover trial for ECT, the optimal dose of succinylcholine and rocuronium mostly oscillates by 0.1 mg.kg, up to 0.2 mg/kg around their optimal effective dose of 50 ($OED_{50\text{-}ECT}$). Therefore we suggest administration of OED50 of either of the NMB agents (succinylcholine 0.85 mg.kg^{-}and rocuronium 0.4 mg.kg^{-}) with dose adjustments based on the quality of the observed motor seizure activity for each individual during subsequent treatments. 0.1-0.2 mg.kg^{-1} increment or decrement in the initial dose should be considered if the corresponding motor activity is insufficient or excessive, respectively. Due to short duration of action and fastest recovery from induced neuromuscular block, succinylcholine is recommended as the first choice with consideration of rocuronium as an alternative. Consistently, Bryson et al. recommended the single bolus dose of succinylcholine 0.9 mg.kg^{-1} for ECT, however they observed high variability among their subjects the fact that highlights our suggested clinical guideline. [9] To improve the perioperative and anesthesia recommendations for ECT provided by the guidelines of the Nederlandse Vereniging voor Psychiatrie (Richtlijnen Nederlandse Vereniging voor Psychiatrie, tweede, herziene versie, 2010), our data suggest using succinylcholine 0.6-0.8 mg/kg for those who might have relative risk of hyperkalemia as initial dose and adjustment of the dose based on the clinical outcome, i.e. any adverse effect due to hyperkalemia and induced level of neuromuscular blockade. For those who have absolute contraindication to succinylcholine or if anesthesiologist in care advise so, e.g. elderly at high risk of developing hyperkalemia due to immobilization or their medications, we suggest using rocuronium 0.4 mg/kg as an alternative initial dose with subsequent dose adjustment as needed. We also recommended applying neurotransmission monitoring to facilitate inducing the optimal seizure activity. Furthermore, quantitative NMT monitoring is highly recommended to evaluate adequate level of relaxation and safe recovery of patients undergoing ECT. NMT monitoring helps to avoid increased risk of adverse respiratory events and overcome the potential inter-individual variability in time to recovery. [3, 26] ECT should be applied after observing

stabilized twitch suppression more that 90% or 1.4 or 3 min (succinylcholine and rocuronium, respectively) for achieving more than 90% peak effect, if monitoring is not available. In the absence of monitoring, clinicians should ensure that patients stay under close observations by appropriately trained personnel in using bedside tests such as tongue depressor test to assess the adequate recovery of neuromuscular function until complete recovery of the neuromuscular transmission. [27] Our study also provided the gourd for a prospective clinical trial using the ED50, OED90 and OED95 of succincylcholine and rocuronium to achieve a better estimation of EC90 and ED95 of these two neuromuscular blockers for application in ECT.

In the follow-up PK-PD study on the ECT data and in *chapter four*, we identified similar pharmacokinetic-pharmacodynamic parameters (k_{e0} and Ce50) for succinylcholine during ECT as previously investigated. For rocuronium the estimated k_{e0} is consistent with others' finding, while we identified higher Ce50 at adductor pollicis that might justify the faster observed recovery from rocuronium induced NMB in this study. This observation warrants further investigation for PK-PD investigation of rocurnium during ECT in a prospective clinical trial.

Pharmacogenetics in ECT: From safety to efficacy

Variation of treatment response and adverse effects of treatment are dependent on genetic factors. The aim of pharmacogenetics is to help to predict an individual's drug response (*prediction of efficacy*), unraveling the potential genetic association *(mechanisms in efficiency of ECT*) while minimizing the side effects (*improvement of safety*). Investigating the effect of treatment on neurotransmitter concentration or receptor function might help in better understanding of the mechanism of ECT treatment. However, the addition of functional genomics by considering the interactive biological effect of genes as well as their protein expressions in response to ECT treatment, may lead to the development of novel and safer medications that mimic the effect of ECT. In *chapter five,* we discussed this point of view for safety of ECT and explored the potential interaction of genes that has been investigated in association with the efficacy of ECT.

Earlier in this section, we discussed in *chapter three* that the inter-individual variability in *BCHE* expression might cause higher variability in applied optimal doses as compared to a non-depolarizing NMB agent such as rocuronium with a different metabolic degradation pathway. Polymorphisms could be clinically important when a medication is dependent on a polymorphic enzyme for metabolism. In *chapter five,* we discussed how genetic variation in the *BCHE1* gene leads to variant enzyme forms, which affects the substrate behavior and results in reduced or absence of the enzyme BCHE activity. This deficiency results in

prolonged post-succinlycholine apnea due to markedly decrease in plasma cholinesterase activity. [28] While clinicians should be aware of this adverse event, currently routine test due to low prevalence of the clinically deficient subjects is not recommended. However, for those patients who exhibit prolonged apnea to succinylcholine, it is important to screen other family members to determine their risk of atypical serum cholinesterase. From the safety perspective of ECT, in this chapter, we also explored other genes such as *CACNA2D1* and C*ACNA1S*, and *RYR1* that are associated with malignant hyperthermia and safe practice of anesthesia in ECT. The reported incidence of MH during ECT has been less than other procedures requiring general anesthesia, a report that requires further investigation.

The neural and the molecular pathway alterations induced by ECT stimulus might explain the mediation of the behavioral changes by this procedural treatment. These alterations are both acute and chronic. While the acute neurotransmitter changes cause the rapid response to treatment, the duration of therapy outcome is in part dependent on the continuation of at least some those acutely induced neurobiological effects. In *chapter five,* we reviewed the evidences that support these neurobiological responses and how the pharmacogenetics or pharmacogenomics might contribute in identifying the neural and the biological pathways involved in the efficacy of ECT or even safety of ECT (e.g. cognitive side effects) as well as predicting the outcome of the therapy. Accordingly, we showed that few studies had investigated gene expression signatures (co-expression of several genes) in response to ECT stimulus. Altar et al.'s pre-clinical investigation, on the effects of single versus repeated electroconvulsive seizure (ECS) exposure on gene transcription to identify genes and potentially associated biochemical pathways with response ECT, was the major study to show the overlap of regionally expressed genes in acute and chronic treatments. [29] They showed that almost one hundred and twenty hippocampal and frontal genes were differentially expressed (e.g. BDNF-MAP kinase) within distinct pathways in response to acute and chronic ECS. Of those, only nineteen genes showed similar expression in response to acute or chronic ECS. In contrast with this approach of investigation, several other studies used a prior knowledge on a gene which directly or in directly may play a role in neurobiological mechanisms to investigate their role in efficacy of ECT response. These studies used either gene polymorphism to predict the therapeutic outcome of ECT or altered transcriptional expression of gene of interest to infer the potentially involved neurobiological pathway. This way, we identified several investigated genes in association with response to ECT treatment. These genes include *BDNF, COMT, DDR2, DDR3, CREB, VEGF, COX-2, TRKB* and NMDA receptor. Accordingly these genes could be assumed as set genes that their potential co-expressions in specific regions of brain might contribute to treatment response. We examined this hypothesis by building the regulatory network of these genes and test if these genes are significantly enriched in a specific region of brain and as part of the known brain functional

regulatory networks. Accordingly, we identified our genes of interest to be prominently enriched in frontal functional regulatory networks. We also consistent with prior studies found that AP-1 transcriptional complex could play an important role in such regulatory networks associated with ECT therapeutic responses, particularly the long-term response. [30] Acquiring such knowledge on the biological mechanisms involved in ECT will provide clues to unraveling the neurobiological alterations that are linked to treatment response and identification of potential targets for novel psychotropic treatments. This attempt is important knowing that ECT is still a physical intervention and more cumbersome than medications with higher efficacy. Although all the above conclusions have to be clinically validated in further studies, there is no doubt that by improvement of the growing technology of functional genomics, large-scale gene and protein expression could provide new insights in how ECT might differently help in treatment psychiatric disorders and which neurotransmitters are more related to the efficacy of treatments. Such detailed knowledge will have profound effects on the diagnosis of psychological disease subtypes, prevention, and treatment of these diseases. In agreement with Palfreyman et al. [31], in *chapter five,* we suggested the comparison of the disease and treatment gene signatures (e.g. antidepressants, ECT, depression) to identify genes or their potential biologically relevant functional pathways which are common between phenotypes of interest. The comparison of the spotted genes could identify a set of targets whose alteration might be a better predictor of disease and the effect of treatment, either by procedure or drug. This approach also provides the opportunity of simultaneously studying the disease, medication used for its treatment and the effective procedural treatment when those medications are not effective. Ultimately, such overlapping genes could be used to identify drug compounds that show similarity in inducing the gene expressions, which consequently mimic the therapeutic response of ECT. As our investigation demonstrates, most of the ECT studies on efficacy of ECT are pre-clinical and further well-designed longitudinal clinical studies are required to increase our knowledge of the mechanisms underlying the efficacy of ECT.

The variability in drug response is highly complex however, and genetic factors has been recognized as one the factors that might influence both the efficacy of a drug and the likelihood of adverse reactions. Applications of pharmacogenetics include the identification of new drug targets, prediction of efficacy and toxicity for new drug therapy, testing for the direct influence of an agent on a specific pathway, and identification of drug responders, nonresponders, and toxic responders within a population. With the advent of pharmacogenetics 'the melding of sciences, including genetics, biochemistry, and molecular pharmacology' has come the hope of personalized medicine in the future. Although medicine may be far from realizing that goal, there has been much scientific progress leading to the hope of one day attaining personalized medicine.

Owing to its importance, CYP2D6 is the most extensively studied P-450 isoenzyme in psychiatry. CYP2D6 enzyme, in part, executes the oxidative metabolism of most of antidepressants (ADs), depending on the metabolizing categories and type of drug. The presence of allelic variants in CYP enzymes with varying degrees of functional significance may result in three main phenotypes, poor metabolizers (PMs), normal metabolizers (NMs), and extensive metabolizers (EMs). The PMs lack an active form of the expressed enzyme due to an inactivating allelic variant; NMs have at least one copy of an active gene; and EMs contain duplicated or amplified gene copies, thus leading to either increased (maybe toxic) or decreased (maybe ineffective) concentrations of the drug. [32] Hence, in *chapter six* we investigated the CYP2D6 enzyme phenotype in prediction of patients underwent ECT. In this study, frequency of CYP2D6 phenotypes was not associated with failure of antidepressant treatment response. CYP2D6 enzyme, in part, executes the oxidative metabolism of most of SSRIs, depending on the metabolizing categories and drug-by-drug basis. The observed frequency of UM phenotype was 0 as opposed to the previously reported prevalence of 3% o in the Dutch population. [33] The prevalence of PMs in ECT patients and patients with single episode of depression were 5.3% and 6.4%, consistent with previous reports (5.5%-9%) in healthy Dutch volunteers. [34-36] The frequencies of IMs in both ECT patients and those with single episode disorders of depression were higher than healthy subjects. [36] Consistently, Haber et al. demonstrated that Hungarian patients with difficult-to-treat depression did not exhibit an increased frequency of aberrant CYP2D6 phenotypes. [37]

Several studies have demonstrated that poor, intermediate and ultra-rapid CYP2D6 metabolizers might have a higher incidence of adverse effects when taking CYP2D6-dependent AD and more risk of TRD. [38] However, an almost equal number of studies did not find significant evidence to support these findings. [38] In line with these evidences, our study does not support the routine application of *CYP2D6* genotyping prior to treatment to reduce the risk of non-responsiveness to the CYP2D6-dependent ADs. Our study has the advantage that the unipolar and bipolar depressive patients in each of the study groups represent extreme clinical outcomes of depression, i.e., one group of patients with severe and recurrent episodes who had received several prior trial treatments, eventually indicated for ECT, and the other with only a single episode of depression. However, this fact should also be considered that lack of the CYP2D6 phenotype correlation with failure of AD treatment response might be due to unreported smaller effect size affecting the study power. Accordingly, a large sample size may be required to capture substantial number of CYP2D6 phenotypes and such a presumptive effect size ($N \approx 1000$ for $df=2$ or 3, effect size of 0.1 at $\alpha=0.05$ and $\beta=0.20$). While our results are suggestive that preemptive genotyping for *CYP2D6* currently appears to have no clinical implications in depressed patients undergoing ECT, further large-scale prospective clinical trials are warranted to validate this suggestion.

It is noted that the guidelines of the Nederlandse Vereniging voor Psychiatrie (Richtlijnen Nederlandse Vereniging voor Psychiatrie, tweede, herziene versie, 2010) does not currently provide any recommendation on the impact of pharmacogenomics (PGx), particularly the utility of *CYP2D6* genotyping, in patients with treatment-resistant depression undergoing ECT. An update on the standpoint according to the current evidences is suggested.

The variability in drug response is highly complex however, and genetic factors has been recognized as one the factors that might influence both the efficacy of a drug and the likelihood of adverse reactions. In *chapter six* no increase in prevalence of aberrant genotype-predicted CYP2D6 phenotypes was observed among patients who received ECT for continuation of depression treatment as compared to patients with single episode of depression. However, we found that some clinical characteristics of patients are associated with the indication of ECT for treatment resistant depression. The failure of gender to be associated with the depression recurrence and preferential response to SSRI medication in our results are consistent with previous studies. [39] Older adults might have higher likelihood of receiving ECT for treatment of depression. [40] Similarly, Our data show that patients who received ECT for the treatment of resistant and recurrent depression were older than patients with single episode of depression. Our data also suggest that patients with bipolar depression have a higher risk of receiving ECT than those with unipolar depression. Relevantly, Ghaemi and colleagues studied the outcomes of antidepressant trials for 41 patients with bipolar depression and 37 with unipolar depression matched by age and sex distribution. They found that short-term nonresponse was more frequent in bipolar (51.3%) than unipolar (31.6%) depression. [41] While our results are suggestive that preemptive genotyping for *CYP2D6* currently appears to have no clinical implications in depressed patients undergoing ECT, further large-scale prospective clinical trials are warranted to validate this suggestion.

Advancement of safety of anesthetics for ambulatory procedures

After the introduction of propofol (2,6-di-isopropylphenol), this anesthetic became widely used for induction of general anesthesia and for sedation in intensive-care patients. In recent years, propofol has increasingly been administered for sedation during short diagnostic or treatment procedures such as gastrointestinal endoscopy ECT procedures. In comparison with conventional sedation using short acting central nervous system sedatives such as midazolam, propofol has attractive characteristics to be applied for short procedural sedations; namely a considerably more rapid onset of minimum residual sedation after the procedure. [42]

Although propofol results in a rapid recovery time and widely used in ECT and other medical procedures, adverse hemodynamic and respiratory effects are observed. [43] Sedation with

propofol is often associated with a significant decrease in arterial blood pressure especially in patients with advanced age, higher ASA (American Society of Anesthesiologist) physical status class>II and prior hypotension. [44] Adverse effects on hemodynamic function may occur whenever sedative and analgesic agents are administered.

ECT plays an important role in the treatment of late life depression and other psychiatric conditions in the elderly. Compared to pharmacologic treatments, ECT is administered in high proportion of elderly patients. [45] Therefore, any potential drug-drug interaction that might exacerbate the propofol-induced hypotension during induction of anesthesia could be of high importance for clinicians and should be assessed. Practitioners providing procedural sedation should have a thorough knowledge of the pharmacology of the applied agents and always be cautious on observation of anesthetic adverse effect exacerbation. Potential adverse effects of these agents on airway patency, respiratory function, and hemodynamic balance should be fully appreciated. As an example of such exacerbated adverse events, in *chapter seven,* we introduced a new drug-drug interaction, i.e. propofol induced profound hypotension during induction of anesthesia in patients with rifampin pre-treatment. We demonstrated that the risk of a prolonged hypotensive episode increased almost three-fold when propofol was used for induction in patients who received rifampin. In 40% of subjects, this exaggerated hemodynamic response required vigorous treatment with vasopressors and fluids as well as repeated doses of vasopressors. In our appropriately designed study with control groups, we also considered several other factors such as the duration of fluid abstinence among subjects [46], the dose or type of pre-induction anxiolytic agent, and applied fentanyl doses that might affect the investigation. However, the observed hemodynamic response was significantly greater in the propofol-rifampin group, suggesting a drug-drug interaction as the cause. Hemodynamic instability was not seen when rifampin was given with thiopental, indicating that the interaction is unique to propofol. The potential mechanisms to explain this observation needs to be further investigated. Intravenous administration of rifampin alone can induce hypotension by a direct, dose-dependent reduction of vascular tone and SVR, [47] and propofol-induced hypotension is largely due to venodilation. [48] One potential mechanism might be rifampin augmentation of the venodilating effect of propofol through an increased endothelial production and release of nitric oxide (NO). [49] This may occur as a result of increased NO production by upregulating iNOS mRNA transcription. [50] Rifampin is commonly used for treatment of tuberculosis and less often for prophylaxis of staphylococcal infections and nisseria meningitidis infections. Clinicians should be aware of this potentially dangerous interaction and if patient who is taking rifampin is necessary to undergo medical procedures and consider using alternative agents for induction of anesthesia. A prospective study is desirable to investigate the mechanism of this drug-drug interaction.

Procedural sedation, which includes medications and monitoring, aims to facilitate the performance of the procedures that might cause discomfort such as pain, anxiety, unpleasant memories associated with such procedures. In the ambulatory setting, the optimal anesthetic techniques would provide ideal procedural conditions and rapid recovery with minimizing the side effects of anesthetics. An optimal ambulatory anesthesia will increase the efficiency and reduce the preoperative complications as well as the healthcare costs. Several clinical factors causes delays in post anesthesia care unit (PACU) discharge that significantly increase the cost of ambulatory procedure. [51] In the purview of ambulatory anesthesia efficiency, in *chapter eight*, we investigated the postoperative hemodynamic adverse events and potential contributors to the prolonged PACU discharge after spinal anesthesia. While recovery from the residual motor and sympathetic blockade is primary factor for discharge delay after spinal anesthesia, back pain, post-dural ponctural headache and radicular irritation have been other concerns. [52] Hypotension has been reported to be present after spinal anesthesia in almost in 5.4% patients. [53] The incidence of bradycardia has been shown to be associated with position that the spinal anesthesia was inserted. In one study the incidence of severe bradycardia in the PACU was significantly higher in patients in the Trendelenburg position (60%) than in the horizontal (20%) or hammock (10%) position. [54] The combination of bradycardia and hypotension could cause potential life-threatening hemodynamic instability after spinal anesthesia. Therefor in *chapter eight*, we attempted to determine the coincidence of hypotension and baradycardia after spinal anesthesia as well as to identify factors associated with these hemodynamic changes. We further examined the association of potential dependent variables with increased PACU length of stay and its duration. The coincidence of bardycardia and hypotension was 5% of the patients recovering from spinal anesthesia and was associated with a prolonged PACU length of stay. Among the potential associated factors, the patient's position during spinal placement and the postoperative opioid dose were correlated with the events.

Discharge criteria for patients after spinal anesthesia should minimize the risk of central nervous system or cardio-respiratory depression after discharge. After spinal anesthesia patients are often discharged from the PACU after recovery for motor and sensory function. In this study the severe hemodynamic events occurred even in the absence of profound motor block. Accordingly, this observation on late occurrence of severe hemodynamic instability is suggestive of considering the addition of the orthostatic stability discharge criteria [55, 56] to recovery of sensory and motor function. Modifications of procedural sedation guidelines for patients with high risk of developing such events after spinal anesthesia are also recommended as a preventive measure. Further studies are required to define and test optimal clinical criteria for safe transfer of patients after spinal anesthesia.

FUTURE DIRECTIONS

Safety

In this dissertation we investigated several safety aspects of ECT as a procedural treatment. We defined the minimal effective doses (MEDs) of two NMBA, i.e. succinylcholine and rocuronium for ECT. Accordingly, we suggested a guideline for clinicians how to use ED_{50ECT} (50% effect dose for ECT) of these two NMBA to attain the optimal effective dose (OED) for each patient resulting in an acceptable induced seizure during his/her ECT. We also provided the 90^{th} and 95^{th} percentiles of MEDs for succinylcholine and rocuronium in our results. In our study ED_{50}s were calculated with averaging the mid-point doses of all independent pairs of patients involving a crossover as per methodology of up-and-down adjustment. When using the up-and-down methodology the starting dose should ideally be the minimum dose expected to result in a positive response, i.e., close to the expected ED_{50}, what we considered in our study. This approach results in a obtaining a more precise estimation of ED_{50ECT}, however, any estimated ED_{95ECT} by probit regression using the obtained data from this approach could be inaccurate. A future clinical study could address this issue by applying some fix doses (e.g. $ED_{25ECT,}$ ED_{50ECT}, 90^{th} and 95^{th} percentiles of MED_{ECT}s) using the obtained knowledge from our study to precisely define the ED_{95ECT} of succinylcholine and rocuromium. Furthermore, the observed faster recovery time after using rocuronium during ECT and higher estimated Ce50 for rocuronium in our PK-PD analysis is a matter of further investigation to understand the potential involved mechanisms and other potential factors such as longer duration of seizure or different effect of increased CO during ECT on rocuronium Ce50.

To Advance the safety of anesthetics for ambulatory procedure such as ECT, we investigated severe hemodynamic changes resulted from a newly introduced drug-drug interaction (rifampin-propofol) and factors related to the type of procedures. While clinicians should be aware of these potential drug-drug or periprocedural side effects, the findings require more rigorous future investigation for the validity and mechanisms involved.

Efficacy

To investigate the role of pharmacogenetics in the efficacy of ECT, we searched for the studies used either gene polymorphism to predict the therapeutic outcome of ECT or altered transcriptional expression of genes of interest to infer the potentially involved neurobiological pathway. We identified several genes in association with response to ECT treatment. These genes include *BDNF, COMT, DDR2, DDR3, CREB, VEGF, COX-2, TRKB* and NMDA receptor. Using the network analysis, we showed that the potential co-expressions of these genes in specific regions of brain might contribute to treatment response through building

the functional regulatory network. We also consistent with prior studies found that AP-1 transcriptional complex could play an important role in the identified regulatory networks associated with ECT therapeutic responses. All these genes and their potential co-regulation by common transcriptional factors should be further investigated in future preclinical and clinical studies. There is no doubt that by improvement of the growing technology of functional genomics, large-scale gene and protein expression could provide new insights in how ECT might differently help in treatment psychiatric disorders and which neurotransmitters are more related to the efficacy of treatments. We also studied the application of *CYP2D6* genotyping prior to treatment and its potential role to reduce the risk of non-responsiveness to the CYP2D6-dependent medications. Our study does not support the routine application of this test prior to treatment. However, this observation should be further investigated in a larger prospective randomized trial to satisfy the possibility of unmeasured confounders as well as the potentially smaller effect size of aberrancy of *CYP2D6.* Such a study also provides the opportunity of validating the effect of clinical characteristics such as age and type of depression in prediction of the treatment outcome.

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SUMMARY

Electroconvulsive therapy (ECT) is the transcutaneous application of small electrical stimuli to the brain to produce generalized seizure for the treatment of selected psychiatric disorders, mostly treatment resistant depression, acute mania, and schizophrenic syndromes. ECT has evolved into a widely recognized treatment modality in the practice of psychiatry such that today, ECT is worldwidely administered to an estimated one million patients a year. Safety of ECT increases the efficacy of therapy and provides fulfillment of a series of required treatments resulting in longer treatment effect of ECT. During the last few decades, researchers have been attempting to identify and improve the effectiveness of ECT, to learn how and why it works, to understand its risks and adverse side effects, and to determine the best treatment technique. As a result, the safety and efficacy of ECT has been improved and its indications have been relatively defined to increase the efficiency of outcome of therapy. While there has been considerable improvement in safety features, further investigation have been done to promote both the safety and efficacy of the treatment. Such efforts could also increase our knowledge on the biological mechanisms involved in effectiveness of ECT that might result in discovery of new treatments. In this dissertation, we investigate how preprocedural medications could improve the safety and efficacy of ECT and further investigated the potential role of pharmacogenetics in the efficacy of ECT and procedural side effects such as cognitive disorders.

Chapter one contains a general introduction and describes the current concept of electroconvulsive therapy (ECT) and its aim to induce a therapeutic tonic seizure with the minimum required energy, tailored to the condition of each patient. This chapter provides an overview of the safety and efficacy of ECT depicts the general schema of this dissertation in investigation of the role of clincial pharmacology and pharmacogenetics in improvement of the safety and efficacy of ECT.

Chapter two reviewes the current concepts of neuromuscular blocking agents (NMBA) application for ECT. Anaesthesia and neuromuscular blocking agents (NMBAs) are required to ensure patients' safety during ECT. The optimal dose of muscle relaxant for ECT reduces muscle contractions without inducing complete paralysis. Slight residual motor convulsive activity is helpful in ascertaining that a seizure has occurred, while total paralysis prolongs the procedure unnecessarily. This chapter reviews the current NMBAs and their applied doses for ECT and the potential gap in knowledge for an ideal NMBA during ECT.

Chapter three describes a conducted crossover, assessor-blinded, prospective randomized study to study the optimal effective dose of succinylcholine and rocuronium for ECT.

Succinylcholine or rocuronium were randomly administered in 227 ECT sessions to 45 patients. The initial dose was incrementally increased or decreased by 10% based on two psychiatrists' (blinded to treatment) assessment of 'acceptable' or 'not acceptable' control of evoked muscle contractions (sufficient vs. insufficient or excessive paralysis). The optimal effective doses of succinylcholine and rocuronium in 50% of patients (OED_{50}) were 0.85 $mg.kg^{-1}$ (95% CI: 0.77-0.94) and 0.41 $mg.kg^{-1}$ (95% CI: 0.36-0.46), and the 90^{th} percentile of the applied optimal doses (OED_{90}) 1.06 $mg.kg^{-1}$ (95% CI: 1.0-1.27) and 0.57 $mg.kg^{-1}$ (95% CI: 0.51-0.62), respectively. The inter-individual variability of the OED_{50} (coefficient variation) was 1.24-fold greater for succinylcholine than rocuronium.

Chapter four presents a follow-up study on chapter three to analyze the pharmacokinetics-pharmacodynamics (PK-PD) relationship of succinylcholine and rocuronium during ECT. In this study the data on the first twitch height (T1) of 31 patients who underwent ECT as well as the corresponding intravenously applied doses of succinylcholine and rocuronium were used for the analyses in the study using NONMEM. The PD model parameter estimates for succinlcholine and rocuronium during ECT were k_{e0}= 0.04 min^{-1} (SEE=0.004) and k_{e0}= 0.17 min^{-1} (SEE=0.19), respectively. The Ce50 estimations for these two NMBAs were amounted to 0.7 µg/ml (SEE=0.06) and 1.6 (SEE=0.1), respectively. The Ce50 of neostigmine was measured to be 0.412 (SEE=0.06). The results showed that the estimated PK-PD parameters for succinylcholine and rocuronium during ECT are almost comparable to previous PK-PD estimates for these two NMBA. According to the observed higher Ce50 for rocuronium in this analysis, we suggested this observation might explain faster recovery after ECT from NMB and proposed further investigation.

Chapter five discusses the clinical insights into pharmacogenetics of ECT and adjunctive medications and how the acquired knowledge could improve safety and efficacy of ECT in the indicated patients. This chapter also describes the role of pharmacogenetics in leading to the identification of novel treatments in psychiatric disorders through understanding of potential molecular and biological mechanisms involved. Our review demonstrates that the knowledge for safe application of ECT has been improved, at least partly due to the role of pharmacogenetics in application of anesthetic agents. Some genes such as *CACNA2D1* and C*ACNA1S*, *BCHE* and *RYR1* are associated with safe practice of anesthesia in ECT. We identified several genes (i.e. BDNF, COMT, DDR2, DDR3, CREB, VEGF, COX-2, TRKB and NMDA receptor) that might interactively play important roles in treatment response to ECT. These genes are co-expressed as part of transcriptionally regulatory sub-networks in the brain. In these sub-regulatory networks,

AP-1 transcription including CREB demonstrated the most regulatory effects on the network

objects.

Chapter six reports an investigation on the accumulation of aberrant *CYP2D6* genotypes and predicted metabolizer phenotypes (UM, IM, and PM) in depressive patients indicated for ECT compared to patients with single episode of depression. 76 Dutch Caucasian subjects with unipolar or bipolar treatment resistant depression who underwent ECT were genotyped using Amplichip® CYP450 Test for *CYP2D6* and 208 patients with single episode of unipolar or bipolar depression were used as controls. The result showed that there was no difference in prevalence of CYP2D6 phenotypes (PM, IM, EM and UM) between the ECT and control patients (5.3%, 38.7%, 56.0% and 0.0% vs. 6.4%, 51.0%, 42.6% and 0.0%, respectively). The types of depression (OR=0.33, p=0.018) and age (OR=1.55 for a-10-year increase, p<0.001), but not CYP2D6 phenotype or activity score were associated with the response to antidepressant treatment. In conclusion, preemptive genotyping for *CYP2D6* currently appears to have no clinical implications in treatment resistant depressive patients indicated for ECT.

Chapter seven describes a case report on occurrence of profound hypertension during the induction of general anesthesia with propofol, potentially due to interaction with rifampin. The conducted retrospective data analysis on series of similar cases demonstrated that the risk of a prolonged hypotensive episode increased almost three-fold when propofol rather than thiopental was used for induction in patients who had received rifampin. Almost 40% of cases showed exaggerated hemodynamic responses that required vigorous treatment with vasopressors and fluids. The applied dose of phenylephrine was significantly greater in the propofol-rifampin group vs. control groups, i.e. propofol alone and thiopental and rifampin (p=0.039). The mechanism for this interaction was not investigated and is unknown. Intravenous administration of rifampin alone can induce hypotension by a direct, dose-dependent reduction of vascular tone and systemtic vascular resistance (SVR). Propofol-induced hypotension is largely due to venodilation and rifampin might augment this effect as a result of increased NO production by upregulating iNOS mRNA transcription. While this study reemphasizes that clinicians should be vigilant for the reported drug-drug interaction during procedural treatment, it suggests a prospective study to investigate the mechanism of this drug-drug interaction.

Chapter eight describes a prospective observational investigation on hemodynamic clinical factors that cause delays in post anesthesia care unit (PACU) discharge. 232 consecutive patients were evaluated for postoperative hemodynamic adverse severe events (PHASE, simultaneous severe bradycardia and hypotension). Fifteen patients showed severe hypotension and twelve patients with severe bradycardia, resulting in PHASE in ten patients

(5%). PHASE occurred on average 307 ± 82 min after spinal anesthesia with a mean spinal anesthesia level of L1 at the time of PHASE. Insertion of spinal anesthesia in the lateral position (PHASE: 80%, no PHASE: 34%, p=0.030) and morphine dose (20±12mg versus 9±8 mg, respectively p=0.011) were found to be associated with PHASE. In conclusion, PHASE during recovery from spinal anesthesia is associated with significantly increased PACU length of stay, a 60-minute increase in median PACU length of stay.

Chapter nine provides a discussion on several important aspects of safety and efficacy of ECT that were investigated in this dissertation and how the study contents contributes to the existing literature and clinical principals in application of ECT as well as understanding of the role of clinical pharmacology and pharmacogenetics in ECT. Finally, future research directions to improve safety and efficacy of ECT based on acquired knowledge are explored.

SAMENVATTING

Elektroconvulsietherapie (ECT) is het opwekken van een epileptische aanval middels een korte pulsstroom onder algehele anesthesie om psychiatrische ziektebeelden te behandelen. Het wordt vooral toegepast bij de behandeling van resistente depressie, acute manie en schizofrene syndromen. ECT lijkt nog maar weinig op de omstreden therapie van vroeger en heeft zich ontwikkeld tot een algemeen geaccepteerde behandelmethode die naar schatting wereldwijd bij een miljoen patiënten per jaar wordt toegepast. In de laatste decennia hebben onderzoekers geprobeerd het werkingsmechanisme van ECT te ontrafelen teneinde de effectiviteit te vergroten en de bijwerkingen te minimaliseren. Hoewel dit onderzoek heeft geleid tot een significante verbetering van de veiligheid van de behandeling is een verdere verbetering van de veiligheid en werkzaamheid van ECT gewenst. Dit proefschrift beschrijft ons onderzoek naar het verbeteren van de veiligheid en effectiviteit van ECT door middel van optimale toepassing van ondersteunende geneesmiddelen en de mogelijke toepassing van farmacogenetica daarbij.

Hoofdstuk 1 bevat een algemene inleiding en beschrijft de huidige stand van zaken van elektroconvulsietherapie waarbij men met minimale energie, afgestemd op de conditie van de patient, een convulsie tracht te induceren. Dit hoofdstuk geeft tevens een overzicht van de veiligheid en werkzaamheid van ECT en beschrijft de indeling en aanpak van het in dit proefschrift beschreven onderzoek.

Hoofdstuk 2 beschrijft de resultaten van een systematisch literatuur onderzoek naar de toepassing van spierrelaxantia (neuromusculaire blokkers (NMBA)) bij ECT. Om de ECT procedure veilig te laten verlopen is een hypnoticum en een spierverslapper noodzakelijk. De optimale dosering van spierrelaxantia tijdens ECT vermindert spiercontracties maar geeft geen volledige verlamming. Een kleine residuele motorische activiteit is nuttig bij het vaststellen van het optreden van het motorisch insult. Dit hoofdstuk bevat een overzicht van de huidige NMBA's, hun toegepaste doses voor ECT en het mogelijke hiaat in de kennis voor een ideale NMBA tijdens ECT.

Hoofdstuk drie beschrijft de resultaten van een gerandomiseerd, geblindeerd cross-over onderzoek naar de optimale dosis van succinylcholine en rocuronium bij ECT. Succinylcholine of rocuronium werden toegediend gedurende 227 ECT sessies in 45 patiënten. De initiële dosis werd stapsgewijs met 10% verhoogd of verlaagd op basis van de beoordeling (wel/niet acceptabel) van de opgewekte spiercontracties door twee voor de behandeling geblindeerde psychiaters. De optimale dosis succinylcholine en rocuronium in 50% van de patiënten (OED50) was respectievelijk 0.85 $mg.kg^{-1}$ (95% CI: 0.77-0.94) en 0,41 $mg.kg^{-1}$ (95%

CI: 0.36-0.46). Het 90ste percentiel van de optimale doses (OED90) bedroeg respectievelijk 1.06 mg.kg^{-1} (95% CI: 1.0-1.27) en 0,57 mg.kg^{-1} (95% CI: 0.51-0,62). De inter-individuele variatie van de OED50 was 1.24 maal groter voor succinylcholine dan voor rocuronium.

Hoofdstuk 4 beschrijft de resultaten van een vervolgonderzoek op het in hoofdstuk 3 beschreven onderzoek. In hoofdstuk 4 wordt de relatie tussen de farmacokinetiek en farmacodynamiek (PK-PD) van succinylcholine en rocuronium tijdens ECT onderzocht. In deze studie werden de gegevens over de eerste spierrespons (T1) en de bijbehorende doses succinylcholine en rocuronium van 31 patiënten die ECT ondergingen geanalyseerd met NONMEM. De PD parameterschattingen voor succinlcholine en rocuronium tijdens ECT bedroegen respectievelijk ke0=0.04 min^{-1} (ZIE=0.004) en ke0=0.17 min^{-1} (ZIE=0.19). De Ce50 schattingen voor deze twee NMBA bedroegen respectievelijk 0.7 ug/ml (SEE=0.06) en 1.6 (SEE=0.1). De Ce50 van neostigmine bleek 0,412 (ZIE=0.06). De gevonden schattingen voor de PK-PD parameters voor succinylcholine en rocuronium tijdens ECT zijn vergelijkbaar met eerdere schattingen van de PK-PD parameters voor deze twee NMBA. Mogelijk kan het snelle herstel van neuromusculaire blokkade bij ECT worden verklaard door de waargenomen hogere Ce50 voor rocuronium. Verder onderzoek hiernaar is wenselijk.

Hoofdstuk 5 beschrijft een literatuuronderzoek naar de toepassing van farmacogenetica in de behandeling met ECT en de daarbij toegepaste geneesmiddelen om effectiviteit en veiligheid van de behandeling te verbeteren. Dit hoofdstuk beschrijft ook hoe farmacogenetisch onderzoek kan leiden tot nieuwe inzichten in de moleculaire en biologische mechanismen die ten grondslag liggen aan psychiatrische ziekten en daardoor mogelijk kan leiden tot nieuwe behandelstrategieën.

Het literatuuronderzoek laat zien dat de veilige toepassing van ECT mede mogelijk is gemaakt door de toepassing van farmacogenetica bij het gebruik van anesthetica.

Genen zoals *CACNA2D1*, *CACNA1S*, *BCHE* en *RYR1* worden in verband gebracht met veilige toepassing van anesthesie bij ECT. Uit de literatuur blijkt dat transcripties van de genen *BDNF, COMT, DDR2, DDR3, CREB, VEGF, COX-2, TrkB en NMDA receptor* een belangrijke rol zouden kunnen spelen bij reactie op ECT behandeling.

Hoofdstuk 6 beschrijft de resultaten van een onderzoek naar de mogelijk accumulatie van afwijkende CYP2D6 genotypen en afgeleide fenotypen (UM, IM, en PM) bij depressieve patiënten geïndiceerd voor ECT. Hiervoor werden gegevens verzameld van 76 Nederlandse blanke patiënten met unipolaire of bipolaire behandeling resistente depressie die ECT ondergingen en waren gegentoypeerd voor CYP2D6 met de Amplichip® CYP450 Test. Deze werden vergeleken met 208 controle patiënten met een enkele episode van unipolaire of

bipolaire depressie. Er bestond geen verschil in prevalentie van CYP2D6 fenotypen (PM, IM, EM en UM) tussen ECT en controle patiënten (5.3%, 38.7%, 56.0% en 0.0% tegenover 6.4%, 51.0%, 42.6% en 0.0%, respectievelijk). Het type depressie (OR = 0.33, p = 0.018) en de leeftijd (OR = 1.55 voor een verhoging van 10-jaar, p <0.001), maar niet het CYP2D6 fenotype of de activiteitsscore bleken geassocieerd met de respons op antidepressiva. Op basis van de deze resultaten werd geconcludeerd dat preventieve genotypering voor CYP2D6 momenteel geen rol lijkt te hebben in de behandeling van therapieresistente depressieve patiënten geïndiceerd voor ECT.

Hoofdstuk 7 beschrijft een casus van langdurige hypotensie na toediening van propofol in een patient die tevens behandeld werd met rifampicine. Patiënt-controleonderzoek onder 75 patienten bevestigde dat het risico op langdurige hypotensie met een factor van bijna drie toenam indien propofol in plaats van thiopental werd gebruikt bij patiënten die tevens rifampicine kregen. De toegepaste dosis van fenylefrine bleek niet normaal verdeeld en significant hoger in de propofol-rifampicine groep vergeleken met de controles (p = 0.039). Deze studie laat zien dat het belangrijk is alert te zijn op niet eerder beschreven geneesmiddelinteracties.

Hoofdstuk 8 beschrijft een prospectief observationeel onderzoek naar het mogelijk vertragende effect van hemodynamische klinische factoren op het ontslag van de post anesthesie care unit (PACU). In totaal werden 232 opeenvolgende patiënten onderzocht op *Postoperative Hemodynamic Adverse Severe Events* (PHASE, gelijktijdige ernstige bradycardie en hypotensie). Vijftien patiënten vertoonden ernstige hypotensie en twaalf patiënten vertoonden ernstige bradycardie, resulterend in tien patienten met PHASE (5%). PHASE trad gemiddeld 307 ± 82 min na spinale anesthesie op met een gemiddeld niveau van spinale anesthesie L1 op het moment van PHASE. Toepassing van spinale anesthesie in de laterale positie (PHASE: 80%, geen PHASE: 34%, p = 0.030) en morfine dosis (20 ± 12 mg versus 9 ± 8 mg, respectievelijk p = 0.011) waren geassocieerd met het optreden van PHASE. Er werd geconcludeerd dat het optreden van PHASE tijdens het herstel van spinale anesthesie geassocieerd is met een verlenging van 60-minuten van de mediane verblijfsduur op de PACU.

Tot slot worden in **hoofdstuk 9** de resultaten van het uitgevoerde onderzoek bediscussieerd en toekomstperspectieven voor de toepassing van klinische farmacologie en farmacogenetica bij de behandeling met ECT geschetst.

DANKWOORD

First and foremost, I would like to express my sincere gratitude to my advisor, Professor Dr. Henk-Jan Guchelaar, for the continuous support of my PhD study and research, for his patience, motivation, enthusiasm, and immense knowledge as well as providing me with an excellent atmosphere for progress of my research. His guidance and quick responses to my emails helped me in all the time of research and writing of this dissertation. I could not have imagined having a better advisor and mentor for my PhD study. Without his support, encouragement, and dedication to assist me, this dissertation would not have been possible.

Besides my PhD advisor, I would like to specially thank Professor Dr. Albert Dahan and Dr. Jesse Swen and the rest of my dissertation committee for their encouragement, insightful comments, and excellent guidance. My sincere thanks also goes to Erik Olofsen from department of Anesthesiology at Leiden University Medical Center (LUMC) for his assistance and the staff of the department of Clinical Pharmacy & Toxicology at LUMC in Leiden, particularly Ms. Marion Blonk and Ms. Mieke Springer for their help throughout the PhD course.

A special acknowledgement goes to Dr. Ala Nozari in Department of Anesthesia and Critical Care of Massachusetts General Hospital for his support, advice and the continuous encouragement. I take this opportunity to express gratitude to all of the staff of the Post Anesthesia Care Unit of Massachusetts General Hospital for their assistance during the projects and the department faculty members for their help and support.

In particular and full gratitude, I would like to acknowledge my Bioinformatics advisor “Professor Scott T. Weiss” in Channing Division of Network Medicine at Brigham and Women’s Hospital who encouraged, inspired and supported me during my PhD study.

Most importantly, none of this would have been possible without the love and patience of my family. My immediate family, to whom this thesis is dedicated to, has been a constant source of love, concern, support and strength all these years. I would like to express my heart-felt gratitude to my family who has aided and encouraged me throughout this endeavor.

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Hooman Mirzakhani was born and raised in Tehran, Iran. After finishing high school in 1989, he started his study in Medicine at “Tehran University of Medical Science (TUMS)”. He obtained his doctoral degree in 1997 and did his National Service by 2001. He continued to practice medicine in govermental and private hospitals, and Emergency Rooms untill 2008, when he immigrated to United States. In this year, he started his research fellowship at the department of Medicine of Beth Israel Deconess Medical Center, an affilated hospital of Harvard Medical School in Boston, Massachusettes. Passing his United States Medical Licensing Examinations, Hooman joined the Department of Aneshtesia and Critial Care at Massachussetes General Hospital for continuation of his postdoctoral reasearch fellowship in 2010, where he acomplished several clinical studies. He started his PhD projects in 2013 under supervision of Professor dr. Guchelaar at department of Clincial Toxicology and Pharmacology in Leiden University Medical Center in Leiden University in collaboration with Department of Aneshesia, Critical Care and Medicine at Massachusettes General Hospital in Boston, MA, USA. To follow his interests in translational medicine and biomedical science, he enered a postodoctoral training program in Biomedical Informatics at Harvard Medical School. He completed his training in Biomedical Informatics under supervison of Professor Scott T. Weiss at Channing Division of Network Medicine in Brigham Women’s Hospital and attained his Master of Medical Science degree in 2015. Since 2013, he has also acted as a councilor for American Federation for Medical Research (AMFR) to provide guidance to younger researchers and help the AMFR committee in achieving the core objectives of AMFR. Hooman currently lives at Boston and continues his research at Channing Division of Network Medicine of Brigham Women Hospital to enrich his translational and system biology skills. Presently, he is honored to be a United States National Institued of Health (NIH) trainee in the only training program in the Clinical and Genetic Epidemiology of Lung Diseases (T32 HL007427) in US.

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1. **Mirzakhani H**, van Noorden MS, Swen J, Nozari A, Guchelaar HJ. Pharmacogenetics in electroconvulsive therapy and adjunctive medications. *Pharmacogenomics. 2015 Jun;16(9):1015-31.*

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