Dexmedetomidine *versus* Propofol as an Adjunct to Ketamine for Electroconvulsive Therapy Anesthesia

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Abstract

Objectives: Electroconvulsive therapy (ECT) is an effective non-pharmacological treatment for refractory mental illness, where a generalized seizure is induced under general anesthesia. An ideal combination of the anesthetic drugs should keep the patient paralyzed and unconscious for a few minutes, while allowing rapid recovery, supporting peri-procedural hemodynamic and respiratory stability and permitting an effective treatment. We examined whether dexmedetomidine is advantageous over propofol as an adjunct to ketamine during ECT.

Methods: 60 patients were randomly assigned to receive either ketamine-propofol (KP) or ketamine-dexmedetomidine (KD). Periprocedural hemodynamic and respiratory parameters, recovery metrics, seizure length, side effects and cost of treatment were compared between the two groups.

Results: Hemodynamic response, respiratory status and side effect profiles in KD and KP groups were similar. KD combination showed a slight advantage with returning to baseline mean arterial pressure levels sooner. Seizures lasted longer in KD group (41.8 sec vs 25.4 sec, p=0.001). Recovery time was similar in two groups (p=0.292), however time to eye opening and following orders was longer in KD (p<0.001 and p=0.003). The cost of treatment for KD was much higher than KP (p<0.001).

Conclusion: Ketamine-dexmedetomidine induction led to longer seizures during electroconvulsive therapy compared to ketamine-propofol. We observed slightly better hemodynamic stability with dexmedetomidine compared to propofol. Despite dexmedetomidine's disadvantages with a longer duration of administration, possible higher cost and minor delay in initial recovery, it should be considered as a feasible agent for ECT anesthesia.

Keywords:

Dexmedetomidine, Electroconvulsive therapy, Ketamine, None-OR anesthesia, Outpatient Anesthesia, Propofol

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Main points:

- General anesthesia is an essential component of ECT treatment. As ketamine is gaining popularity in psychiatric treatments, adjuncts to use ketamine should be considered
- Combining ketamine with dexmedetomidine led to longer seizures than with propofol
- Hemodynamic stability was better with ketamine-dexmedetomidine compared to ketamine-propofol
- Recovery is slightly longer with dexmedetomidine than with propofol, however discharge to ward time remains the same

Introduction

Electroconvulsive therapy (ECT) is an effective treatment option for treatment-resistant severe psychiatric illnesses. An electric shock-induced generalized seizure alters brain biochemistry and physiology in a way that alleviates severe depressive and psychotic symptoms (1,2). ECT is always performed under general anesthesia to provide the best and safest treatment experience for the patient (2).

ECT is one of the most effective treatments in psychiatry (2). Individual success of treatment depends on several factors that have not yet been clearly identified. Although the length of the seizure has not been linked to treatment success, seizure duration of at least 15 to 25 seconds is desirable (3). If a shorter seizure is observed, a second seizure is induced with measures to prolong its duration or voltage is increased (3). In addition to patient and procedural factors, the anesthetic drugs also affect the seizure activity, hence anesthetic management may be contributary to treatment outcome (4).

Ideal anesthetic drug combination for an ECT case should be fast- and short-acting (5,6). Complete unconsciousness and neuromuscular blockade should be achieved for patients' comfort and wellbeing. If not intervened, physical activity caused by the generalized seizure can lead to soft tissue damage, bone fractures and even nerve palsies. Patients should remain hemodynamically stable and recover quickly without any anesthesia related side effects, such as respiratory depression. Anesthetic drugs should not suppress seizure activity (4). It is challenging to find a drug or drug combination that will hit all these points in all patients, therefore extensive comparison of numerous drugs and their combinations are available in medical literature (5,6).

Ketamine is a non-competitive NMDA agonist and unique among common anesthetic drugs with its dissociative profile (7). It provides analgesia and amnesia while patients' muscle tone, respiratory drive and cardiovascular functions remain unsuppressed (7). Ketamine increases the sympathetic tone on the cardiovascular system, which may be disadvantageous in the setting of ECT (8). Intravenous ketamine use provides quick anesthesia and may also lengthen seizure duration in ECT (6).

Propofol is a short-acting intravenous hypnotic and potentiates the inhibitory activity of GABA-A receptors (7). It achieves loss of consciousness and apnea quickly and is commonly used during ECT despite its anti-convulsant activity (9). Studies show that ECT can remain effective with its use and that propofol suppresses the hemodynamic response to the seizure (6). Its short duration of action

with a single bolus dose allows for a smooth post-ECT recovery (9). Lowest dose possible should ideally be used for longer seizure activity.

Dexmedetomidine is an alpha-2 adrenergic receptor agonist (7). Its intravenous administration leads to anxiolysis, sedation, hypnosis and analgesia without respiratory suppression (7). It can also decrease the sympathetic tone over the cardiovascular system. Its inaction over the seizure activity is ideal for ECT (4). We expect that dexmedetomidine would attenuate ketamine's hemodynamic effects without undermining respiratory stability or quality of seizure activity.

The combination of ketamine and propofol has been studied for ECT extensively. Although better physiological and treatment outcomes in terms of seizure duration are observed, better clinical outcome is not proven yet (8,10–12). In this study we compared ketamine-dexmedetomidine combination (KD) to ketamine-propofol (KP) in the search for the probability of a better anesthetic recipe for ECT.

Materials and Methods

60 patients, ages 18 to 60 years, were enrolled in this prospective, randomized, controlled study after approval of University of Istanbul – Cerrahpasa Clinical Research Ethics Committee (14/11/2018 – 72109855-604.01.01-92505). Informed written consent was obtained from the patients or their legal guardians if the patient did not have the capacity to consent. Exclusion criteria included being American Society of Anesthesiologists (ASA) class III or more, pregnancy, organ

failure, alcohol or other drug addictions, lithium use, low pseudocholinesterase levels, receiving first session of ECT and having glaucoma.

All patients had their anesthetic evaluation at the preoperative anesthesia clinic. After patients arrived to the ECT room, monitors for non-invasive blood pressure, electrocardiogram and peripheral oxygen saturations were applied. A 20-gauge venous cannula was placed on the right arm, freeing the left arm for observing seizure activity with tourniquet application.

Initial measurements of systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), heart rate (HR) and peripheral oxygen saturation (SpO_2) were recorded before any drug administration (baseline). Patients were randomly assigned to ketamine-dexmedetomidine (KD) (n=30) and ketamine-propofol (KP) (n=30) groups with the closed envelope technique. Measurements for a single ECT session were recorded for each patient and each patient was enrolled in the study only once.

KP patients received 1 mg kg^{-1} intravenous (iv) propofol (Propofol, Fresenius Kabi, Austria) injected over 1 minutes and a bolus dose of 1 mg kg^{-1} iv ketamine (Ketalar, Pfizer, Turkey), KD patients received 1 µg kg^{-1} iv dexmedetomidine (Precedex, Abbott, USA) injected over 10 minutes and a bolus dose of 1 mg kg^{-1} iv ketamine. After the anesthesiologist administered these drugs, the psychiatric team were called into the room for ECT. If the patient needed extra anesthetic, we planned to administer 0.5 mg kg^{-1} ketamine. After loss of consciousness, the tourniquet on the left upper arm was inflated to a pressure of 50 mmHg above the SAP. Neuromuscular blockade (NMB) was achieved

with iv injection of 1 mg kg^{-1} succinylcholine. Patients were ventilated with a bag-valve mask attached to 10 L min^{-1} oxygen. 2 minutes after NMB injection, psychiatry physician placed bitemporal electrodes and applied shock as per their usual protocols for ECT (a pulse width of 1 s, pulse amplitude 800 mA, duration between 1-4 s and frequency ranges from 40 to 90 Hz; MECTA spECTrum 5000Q, USA).

The motor seizure duration was timed from the electric shock to the last clonic seizure activity observed in the left arm. Blood pressures, HR and SpO_2 were measured and recorded again after cessation of the seizure (ECT 0), 5 minutes later (ECT 5) and before leaving the recovery area (discharge). Recovery period was assessed with time to eye opening, time to following orders and time to discharge with a Modified Aldrete Score of 8 or above (13). Amount of administered drugs were recorded for cost calculation.

Any adverse reactions observed during ECT procedure and recovery were recorded. Respiratory rate less than 10 min^{-1} was recorded as respiratory depression, SpO_2 less than 90% as hypoxemia, HR lower than 50 min^{-1} as bradycardia, HR higher than 100 min^{-1} as tachycardia and MAP higher than 120 mmHg as hypertension. Nausea, vomiting and agitated behavior were recorded as observed.

For statistical analysis SPSS (IBM SPSS Statistics Version 27) software was used. 30 patients for each group were calculated with an alpha error of 5% and power of 80%. Normal distribution was checked with Shapiro Wilk test, histogram, Q-Q plot and box plot. Mean and standard deviation were used for age, height, weight, MAP, HR and SpO_2. Independent sample t-test was used for

comparison of continuous variables with normal distribution. Mann Whitney U was used for comparison of continuous variables without normal distribution. Variables within a group that changed over the course of the procedure were analyzed with Friedman repeated measures variance analysis. Nominal variables were compared with Chi square test with Yates correction and Fisher's exact probability test. In all previously mentioned tests, $p<0.05$ was accepted as significant. Multivariable comparisons were done with Wilcoxon test with Bonferroni's correction ($p<0.0083$ accepted as significant).

Results

We enrolled 60 patients scheduled for an ECT session in this study. 30 patients were assigned to each group. Distribution of age, height, weight and sex were similar. Group KP had 18 male and 12 female patients, group KD had 15 male and 15 female patients ($p=0.79$). Average age was 45 ± 15 years in KP and 40 ± 17 years in KD ($p=0.12$). Weight and height measurements were 75 ± 16 kg and 169 ± 10 cm in KP and 74 ± 15 kg and 169 ± 7 cm in KP ($p=0.35$ and 0.16, respectively).

We analyzed mean arterial pressure and heart rate to evaluate hemodynamic response and SpO_2 for respiratory changes, and measurements in none of the parameters were normally distributed (Table 1). The change in MAP over the four time points were statistically significant in both groups ($p<0.001$), however the change varied slightly (Figure 1). In both groups, MAP increase from baseline

to ECT 0 and MAP decrease from ECT 5 to discharge were significant (p<0.001), while the change from baseline to discharge was insignificant (KP p=0.781, KD p=0.094). In group KP, no significant change in MAP occurred from ECT 0 to ECT 5 (p=0.382), while in group KD the drop in blood pressure was significant (p<0.001). For the change in MAP from ECT 0 to ECT 5, the difference between two groups were significant (p=0.008).

For group KP, the change in HR over the course of ECT was insignificant (p=0.3). Patients in KD had significant change in HR over the four time points (p=0.035), however in further analysis only the change from baseline to ECT 5 was significant (p=0.006). From baseline to discharge, the heart rate increased in group KP and decreased in group KD and this comparison between groups is statistically significant (p=0.026, figure 2).

The change in SpO_2 over the course of ECT was insignificant in both groups (KP p=0.372, KD p=0.884) and there was no significant difference between the groups.

Table 2 and figure 3 include seizure duration, recovery phase and cost for the treatment. Mean duration of initial seizure activity was 25.4 ± 15.2 seconds in group KP and 41.8 ± 23.0 seconds in group KD with a statistically significant difference between the two groups (p=0.001). 6 patients in group KP did not have adequate length seizures and the mean duration for second seizure was 26.3 ± 9.0 s. 2 patients in group KD did not have adequate length seizures and the mean duration for second seizure was 50.5 ± 50.2 s. The difference in the need for a second electric shock was not statistically significant.

Time to eye opening in group KP was significantly shorter than KD (9.1 ± 3.6 min vs 13.7 ± 4.4 min, p<0.001). Similarly, time the patients took to obey orders was significantly shorter in group KP than group KD (12.1 ± 4.3 min vs 16.0 ± 4.8 min, p=0.003). Time to discharge with a modified Aldrete score of 8 or higher was similar in both groups (19.6 ± 5.7 min vs 21.2 ± 5.6 min, p=0.292). Treatment cost in our institution was significantly higher in group KD than KP (23.4 ± 2.4 TL vs 3.2 ± 0.5 TL per person, p<0.001).

The difference in side effects from the two drug combinations were not statistically significant (p>0.05). In group KP, 5 patients had hypertension, 3 had hypoxia, 2 had nausea and 4 had agitation. In group KD, 5 patients had hypertension, 2 had hypoxia, 2 had nausea, 1 had vomiting and 1 had agitation.

Discussion

Electroconvulsive therapy is an effective therapeutic alternative in modern psychiatry for refractory depressive and psychotic disorders (14). General anesthesia with muscle relaxation is essential for patient safety and wellbeing during ECT, and it should be carefully managed for best treatment outcomes (2). An ideal drug or drug combination should have no influence on seizure quality, be quick acting, provide complete neuromuscular blockade and amnesia and have no side effects (5,6). Providing satisfactory anesthesia for an ECT patient requires a lot of tailoring from anesthesiologist's part. In this study we compared ketamine-dexmedetomidine combination to ketamine-propofol

combination (with succinylcholine as a neuromuscular blocker) for ECT, a comparison we did not find in the literature.

Ketamine is a commonly used agent for ECT with its anti-depressive and dissociative anesthetic profiles and seizure lengthening effect (15). However, ketamine increases sympathetic discharge leading to an increase in heart rate and blood pressure, thus it may complicate a cardiac compromise due to ECT. Propofol is frequently used during ECT as well. Its quick onset of action and metabolism make it ideal for such a short procedure, and its anti-emetic effect can reduce post-ictal nausea (16). Its shortcomings include a decline in heart rate and blood pressure, respiratory depression and a rise in seizure threshold (7,16). A combination of ketamine and propofol has been shown to be effective in various anesthetic settings including ECT (8,17). Ketamine counteracts the anticonvulsant effect of propofol, while the two drugs balance out the opposite hemodynamic effects of each other.

Dexmedetomidine is becoming more popular for procedural use as it is studied further beyond intensive care (18,19). It provides sedation without respiratory depression, does not affect seizure duration and blunts the sympathetic response supporting hemodynamic stability (20). However adequate anesthesia for ECT cannot be achieved solely by dexmedetomidine (21). Sedation is achieved quickly with ketamine-dexmedetomidine combination (KD), while ketamine prevents hypotension and bradycardia associated with dexmedetomidine, and while dexmedetomidine blunts sympathetic drive and decrease psychiatric symptoms associated with ketamine(19). We aimed to

determine if dexmedetomidine may be superior to propofol as an adjunct to ketamine for ECT anesthesia.

Hemodynamic response to ECT typically consists of an initial parasympathetic response lasting 10-15 seconds followed by a sympathetic response. Cardiac complications may include left ventricular dysfunction, acute myocardial infarction, pulmonary oedema, ventricular rupture, arrythmias and asystole, especially in patients with cardiac disease (22). Therefore, a drug combination with smallest hemodynamic effect is desirable. Previous studies showed that ketamine-propofol combination has better hemodynamic outcomes in terms of heart rate and blood pressure stability than propofol or ketamine alone during ECT (8,10). Similarly, a dexmedetomidine-propofol combination was shown to be superior to propofol alone in terms of hemodynamic response during ECT (23). Ketamine was shown to prevent dexmedetomidine induced hypotension and bradycardia for procedural sedation (19).

In our study, we observed an initial rise in blood pressure and reversal to baseline blood pressure level by discharge with both KP and KD patients. The change over the course of the ECT was around 20 mmHg and statistically significant in each group. One noteworthy difference between KP and KD was that KD patients returned to near baseline blood pressure levels quicker, at 5 minutes after seizure activity. This observation is suggestive of better hemodynamic stability with ketamine and dexmedetomidine. Heart rate did not change significantly with KP and there was a slight decrease of 2 beats per minute with KD. Although statistically significant, this change is unlikely to have any

clinical implications. Both combinations showed an equally good and similar heart rate response. Similarly, peripheral oxygen saturation remained unchanged with both combinations.

Recovery from anesthesia during the post-ictal phase tends to be faster with propofol alone than ketamine alone or ketamine-propofol combinations (8,10,24). We observed that time to eye opening and obeying orders were four minutes shorter in KP patients than in KD patients, showing an even longer sedation time due to dexmedetomidine. Nevertheless, time to discharge with a Modified Aldrete score of 8 or higher were similar in both groups. In practice, both combinations require similar patient observation time after ECT.

Side effects after an ECT session include confusion, agitation, amnesia, nausea, headache, respiratory depression and hypertension. The anesthetic drugs contribute to these side effects as well as the induced generalized seizure. Ketamine can cause nausea and agitation and these side effects can be attenuated with propofol (25). Dexmedetomidine is shown to lower incidence of post ictal agitation in ECT patients (20,26,27). Some of our patients had nausea, vomiting, hypoxia, hypertension and/or agitation, however we observed similar rates of side effects in each group.

Studies on anesthetics' effects on seizure length in ECT vary greatly in terms of the drug dosages and combinations. Although seizure duration has not been linked to treatment outcome, suppression of seizure activity by anesthetic drugs is best avoided as a seizure shorter than 25 seconds warrants for induction of a second seizure (3,14). Propofol is associated with shorter seizure duration on a dose dependent fashion, however an unfavorable impact on clinical outcome is not proven (9).

Nevertheless, combining propofol with ketamine can lengthen seizure length (12). In our study KD patients had significantly longer seizures (41.8 sec) than KP patients (25.4 sec, p=0.001). This is a clinically relevant observation as the choice between dexmedetomidine and propofol may be made based on past seizure activity in patients with particularly short or long seizures. Number of patients who did not develop a seizure after the first electric shock was similar in both groups. This observation is in concordance with the previous observations that seizure threshold and seizure duration has a complex relationship in the context of ECT (28,29).

There are several limitations to our study. Although we observed longer ECT induced seizures with KD, we did not compare the clinical outcome. We showed a slight advantage with KD in terms of hemodynamic response, yet we cannot be sure of its clinically significance without measuring clinical signs of cardiac compromise. The time points we took measurements were limited as well. An ideal study would make use of continuous blood pressure monitoring to enable recording of peak or nadir values; a non-invasive method seems to be reasonable for beat-to-beat hemodynamic monitoring during ECT (30). Slow injection of dexmedetomidine is a practical problem. This administration adds 10 minutes to the procedure and this delay may be unacceptable in some centers. We included the noteworthy cost difference in our results; however, we are aware that this is subject to change over time and depending on local drug prices.

We show that dexmedetomidine is a feasible adjunct to ketamine during ECT. KD and KP combinations are comparable in terms of hemodynamic stability, recovery time and side effect profile during ECT. Longer seizures were observed with KD compared to KP. Dexmedetomidine can complement ketamine anesthesia for ECT with its sedative, hemodynamic and convulsive activity profile. We believe dexmedetomidine should be added to armory of anesthetic drugs suitable for ECT, especially in patients with short seizure activity with propofol or contraindications to its use. Conversely, dexmedetomidine could be reconsidered in patients with prolonged seizures after ECT to limit seizure duration.

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Table Legends

Table 1: Mean arterial pressure, heart rate and peripheral oxygen saturation of the patients in groups KP and KD (mean ± SD) and the p value for the change over the course of ECT

	MAP		HR		SpO2	
Timing	KP	KD	KP	KD	KP	KD
Baseline	93.1 ± 16.9	81.6 ± 14.2	86.2 ± 15.8	85.4 ± 17.4	97.8 ± 1.7	99.3 ± 1.1
ECT 0	114.1 ± 23.4	112.9 ± 27.9	89.9 ± 17.2	91.3 ± 25.6	98.6 ± 7.0	99.0 ± 2.0
ECT 5	111.0 ± 21.7	91.9 ± 17.3	93.3 ± 11.4	79.0 ±14.8	98.1 ± 1.3	99.1 ± 1.7
Discharge	93.4 ± 20.9	77.0 ± 10.2	93.0 ± 15.0	83.5 ± 11.7	98.5 ± 1.1	99.0 ± 1.5
p value	*<0.001*	*<0.001*	*0.300*	*0.035*	*0.372*	*0.884*

Table 2: Seizure duration, recovery phase and treatment cost of the patients in groups KP and KD (mean ± SD) and p values for differences between two groups

	Grup KP	**Grup KD**	***p***
First seizure duration (sec)	25.4 ± 15.2	41.8 ± 23.0	p=0.001
Need for second shock (number)	6	2	p=0.129

Time to eye opening (min)	9.1 ± 3.6	13.7 ± 4.4	p<0.001
Time to obeying orders (min)	12.1 ± 4.3	16.0 ± 4.8	p=0.003
Time to discharge (min)	19.6 ± 5.7	21.2 ± 5.6	p=0.292
Cost (TL/patient)	3.2 ± 0.5	23.4 ± 2.4	p<0.001

Figure Legends

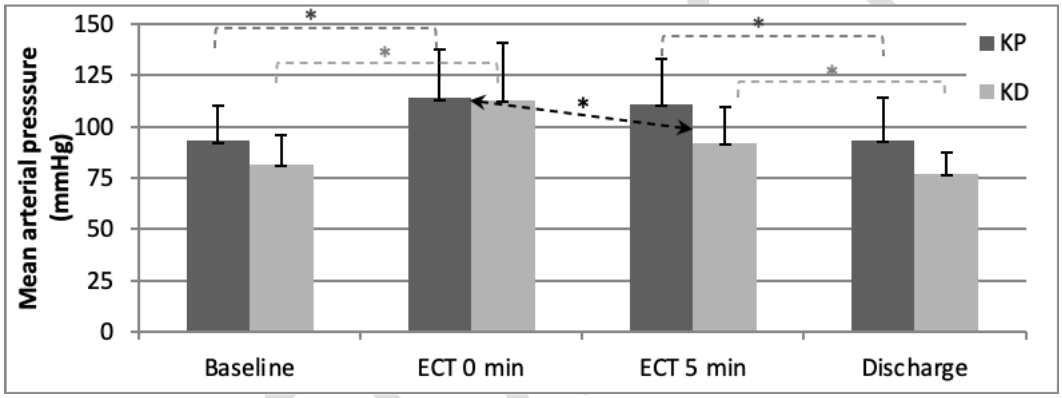

Figure 1: Mean arterial pressures (mean and SD, *: p<0.05). Hemodynamic response to ECT were similar in KP and KD, except from ECT 0 to ECT 5 where KD patients had a significant drop in MAP towards baseline compared to KP patients (arrow).

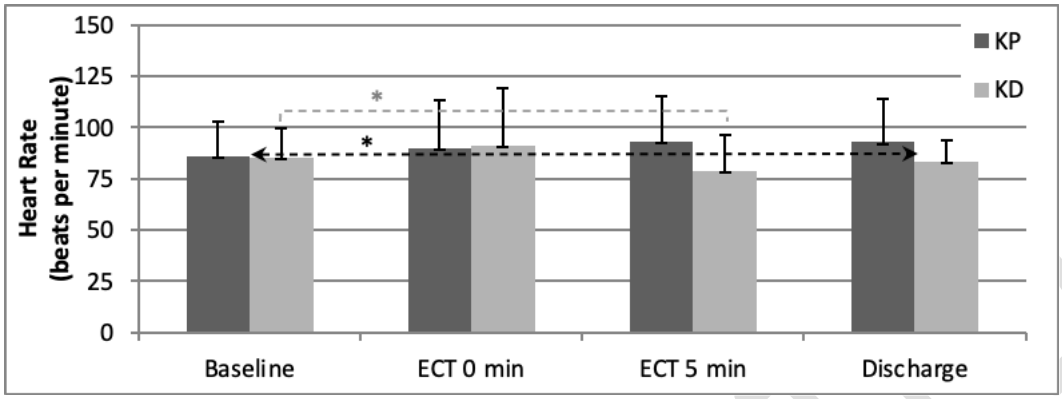

Figure 2: Heart rate (mean and SD, *: p<0.05). Heart rate did not change significantly over the course of ECT in both groups. The difference between the slightly increase in heart rate from baseline to discharge of KP patients and slightly decrease in heart rate (arrow)

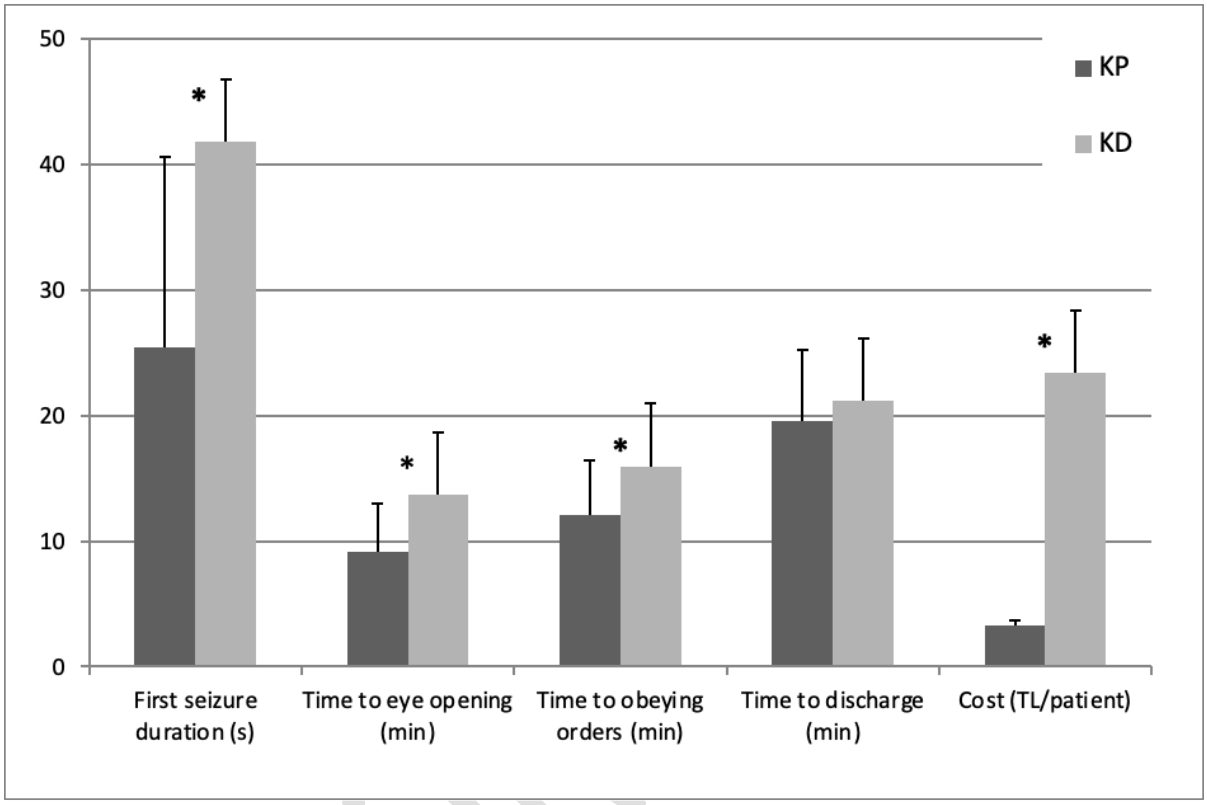

Figure 3: Seizure duration, recovery phase and treatment cost (mean and SD, *: $p<0.05$). Seizures were longer and costs were higher for KD patients. Although KP patients started recovery earlier, all patients were ready for discharge around the same time.

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