Elektrokonvülsif Terapi Sonrası Görülen Baş Ağrısı Tedavisinde Preoperatif Asetaminofen, Deksketoprofen Trometamolün Karşilaştırılması

Comparison of Preoperative Aetaminofen, Deksketoprofen Trometamol on Headache Treatment after Electroconvulsive Therapy

Onur Koyuncu¹, Sedat Hakimoglu², Fabio Rodriguez-Patarrooyo³, Senem Urfalı⁴, Mehmet Hanifi Kokaça⁴, Alparslan Turan⁵

1 Outcomes Research Bölümü, Anesteziyoloji Enstitüsü, Cleveland Clinic, Cleveland, Oh, Amerika Birleşik Devletleri; Hatay Mustafa Kemal Üniversitesi Tip Fakültesi, Psikiyatri Bölümü, Hatay
2 Hatay Mustafa Kemal Üniversitesi Tip Fakültesi, Anesteziyoloji ve Reanimasyon Bölümü, Hatay, Türkiye
3 Outcomes Research Bölümü, Anesteziyoloji Enstitüsü, Genel Anestezi Bölümü, Cleveland, Oh, Amerika Birleşik Devletleri; Cleveland Clinic, Anesteziyoloji Enstitüsü, Genel Anestezi Bölümü, Cleveland, Oh, Amerika Birleşik Devletleri
4 Hatay Mustafa Kemal Üniversitesi Tip Fakültesi, Psikiyatri Bölümü, Hatay, Türkiye

ÖZ

GİRİŞ ve AMAÇ: Elektrokonvülsif tedavi (EKT); mani, şizofreni, akut katatoni gibi ciddi psikiyatrik bozuklukların tedavisi etkili, hayat kurtarıcı ve belirgin yan etkisi olmayan bir tedavi yöntemdir. Baş ağrısı, bu tedavi sonrası yüksek insidsalda (%26-85) görülen ciddi bir komplikasyondur. Bu çalışmada hipotenez, işlem öncesi deksketoprofen trometamol uygulamasının EKT sonrası altı saat içinde baş ağrısı asetaminofendenden daha etkili bir şekilde azaltacağı yönündedir.

YÖNTEM ve GERÇEKLER: Bu prospektif, çift kör, tek merkezli çalışmada, elektrokonvülsif tedavi uygulanan 18 ila 80 yaş arasında toplam 225 psikiyatrik hastayı incelledik. EKT’nin önce üç analjezik stratejisi (1) asetaminofen 1g / 100ml izotonik, (2) deksketoprofen trometamol 50mg / 100ml izotonik; ve (3) 100 ml plasebo intravenöz olarak uygulandı. Baş ağrısı VAS (Vizüel Analog Skalası), kalp hızı, noninvasif kan basıncı, oksijen saturasyonu, solunum hızı, sedasyon (Ramsey Sedasyon Skalası) kullanılarak EKT’den 2 saat 4 saat ve 6 saat sonra değerlendirildi. Analjezik gereksinimleri ve yan etkiler kaydedildi.

BULGULAR: En sık tanı depresyon (% 41), ardından şizofrenik bozukluk (% 38) ve obsesif kompulzif bozukluk (% 21) idi. Baş ağrısı VAS skorları 2 ve 4 saatte gruplar arasında fark bulunmadı, ancak deksketoprofen-trometamol alan hastalarda 6 saat sonra baş ağrısı devam etti. Dördüncü saatte, plasebo grubundaki hastaların % 11’ine diğer iki grubun;karsılıkta analjezi gerekli (p = 0,000).

TARTIŞMA ve SONUÇ: EKT prosedürü sonrası altı saatik dönemde baş ağrısı azalmak için deksketoprofen, asetaminofen ve plasebo fonksiyon etkiliği arasında klinik olarak önemli bir fark bulunmadık.

Anahtar Kelimeler: Asetaminofen, Deksketoprofen trometamol, Elektrokonvulsif Terapi

ABSTRACT

INTRODUCTION: Electroconvulsive therapy (ECT) is an effective, life-saving treatment method with no significant side effects in the treatment of serious psychiatric disorders such as mania, schizophrenia, and acute catatonia. Headache is a serious complication seen with a high incidence (26-85%) after this treatment. Our hypothesis in the study is that pre-procedure administration of dexketoprofen trometamol will reduce headache more effectively than acetaminophen within six hours after ECT.

METHODS: In this prospective, double-blind, single-center study, we studied a total of 225 psychiatric patients aged 18 to 80 years having ECT. Before ECT, three analgesic strategies were used (1) acetaminophen 1g / 100ml isotonic, (2) dexketoprofen trometamol 50mg / 100ml isotonic, and (3) 100 ml of placebo was administered intravenously. Headache intensity using VAS (Visual Analog Scale), heart rate, noninvasive blood pressure, oxygen saturation, respiratory rate, sedation (Ramsey Sedation Scale) were evaluated at 2, 4, and 6 hours after the ECT. Analgesic requirements and side effects were recorded.

RESULTS: The most common diagnosis was depression (41%), followed by schizoaffective disorder (38%), and obsessive compulsive disorder (21%). No difference was found between groups in the headache VAS scores at 2 and 4 hours but patients who received dexketoprofen-trometamol have persistent headache at 6 hours after the procedure. At the 4th hour, 11% of patients in placebo group required rescue analgesia compared to the other two groups (p = 0.000).

DISCUSSION AND CONCLUSION: We found no clinically significant difference between the efficacy of dexketoprofen, acetaminophen, and placebo for reducing headache within the six-hour period after the ECT procedure.

Keywords: Asetaminofen, Deksketoprofen trometamol, Elektroconvulsive Therapy
INTRODUCTION

Electroconvulsive therapy (ECT) was first used by Ugo Cerletti in 1938 for the treatment of a psychiatric patient. (1, 2). It has always maintained its value since it produces a faster response than pharmacological treatment. Major indications for treatment include drug-resistant major depression, mania, catatonia, Parkinson's disease, neuroleptic malignant syndrome, schizoaffective disorder, and schizophrenia (3-5). The main mechanism of action is to provide treatment by creating generalized convulsions by stimulating the brain with electrical current (6, 7).

The incidence of headache after ECT is quite high and is between 26-85% (8-10). The etiology of headache after ECT is not yet fully understood. Possible causes of headache after ECT are thought to be rapid contraction of the temporal and masseter muscles associated with ECT, increased cerebral blood pressure, vasodilatation and alteration of the passage of serotonergic neurons in the brain (3, 9-11). Headache, which occurs immediately or shortly after ECT, may be severe and may have a long-lasting effect. Therefore, patients tend to reject repeated ECT applications. (10, 11). Medical treatment is required in the post-intervention period for the prevention of patients' headache and the continuation of ECT treatment. In the literature, there are studies showing that various intravenous NSA1 drugs and paracetamol are used for analgesia after ECT and positive results are obtained (3, 12). Dexketoprofen trometamol is an effective prostaglandin synthesis inhibitor with rapid onset of action and low gastrointestinal side-effect profile (13). Our hypothesis was that preoperative application of dexketoprofen trometamol will reduce headache more effectively than acetaminophen in postoperative six hours after ECT.

MATERIALS AND METHODS

Study design

After Hatay Mustafa Kemal University Ethics Committee approval (October 2018, approval number 171) and patient written informed consent, we conducted this single-center, double-blind study, and alternating intervention study at Hatay Mustafa Kemal University (Clinical Trials.gov Identifier: NCT02137395).

Two hundred twenty five adult psychiatric patients, between 18 and 80 years old and American Society of Anesthesiologists (ASA) class I-II who underwent ECT procedure were included in our study. We excluded patients with history of hemorrhagic diathesis, peptic ulcer disease, significant cardiac (e.g., coronary artery disease, myocardial infarction, cardiac heart failure.), pulmonary (e.g., chronic obstructive pulmonary disease, emphysema), hepatic (e.g., chronic hepatitis, hepatic cirrhosis) or renal disease (e.g., chronic kidney disease, dialysis requirement); hypersensitivity to any of the drugs used in the study, administration of any analgesics 24 hour before the procedure.

Procedure

Three analgesic strategies (1) acetaminophen (Partemol, Vem İlaç San, Tekirdag, Turkey) 1g/100ml isotonic, (2) dexketoprofen trometamol (Sertofen, Rompharm İlaç San, Tekirdag, Turkey) 50mg/100ml isotonic; and (3) placebo 100ml isotonic intravenous were administered before the ECT. During the 3 weeks study period, patients were weekly assigned to receive one to the three analgesic strategies following the order acetaminophen, dexketoprofen trometamol and placebo.

The patients were routinely monitored (electrocardiogram, peripheral oxygen saturation [SpO2], noninvasive blood pressure, end-tidal carbon dioxide [ETCO2]) in the procedure room. An 18 gauge intravenous catheter was inserted into the forearm vein of the patient. Drugs were given as an infusion 30 minutes before the ECT procedure. Atropine 0.5 mg was administered intravenously to reduce respiratory secretions. Pre-oxygenation was achieved with continuous oxygen flow (100% O2) via a face mask, then anesthesia was induced with 1 mg/kg of propofol (Propofol 2% Fresenius, Graz, Austria). After losing eyelash reflex and consciousness, succinylcholine 0.5-1 mg/kg was administered to the patients. A bite block was used to protect the teeth, lips and tongue from injuries resulting from contraction of the facial muscles of the patient.
When neuromuscular response was completely blocked, ECT was performed by Mecta Spectrum 5000Q (MECTA Corporation, Tualatin, OR, USA) bitemporal electrode stimulation. The dose of electric charge was titrated to approximately 50% of each individual’s seizure threshold and administered as required according to seizure quality during ECT sessions.

To prevent oxygen desaturation, manual ventilation was continued during the clonic phase and maintained until adequate spontaneous ventilation was achieved. The bite block was taken from the patients when seizure activity concluded. The patients were transferred to the recovery room and monitored via ECG and pulse oximetry, and 100% O2 (5 L/min) given to the patient by a nasal cannula, at the end of the procedure. Close monitoring was continued until the patient was awake and reached sufficient oxygen saturation in the room air. After the procedure, if the patient reported a VAS score ≥4 a rescue analgesia with 75mg diclofenac sodium was administered intravenously. If headache persists (VAS score ≥ 4) 20 minutes after the first rescue analgesia administration, 0.25mg/kg tramadol intravenous was given. Patients with nausea and vomiting were given intravenous ondansetron 4mg.

Measurements

We recorded demographic data and duration of the ECT. Postoperative measurements were conducted by a research assistant who was blinded to group allocation. Patients were educated about how to use a Visual Analog Scale (VAS) tool consisting of a 10-cm-long ruler and a marker that patients moved to a point indicating their pain intensity; 0 cm was designated no pain, and 10 cm as the worst ever imaginable pain. Headache intensity using VAS, heart rate, noninvasive blood pressure, oxygen saturation, respiratory rate, sedation (Ramsey Sedation Scale), were evaluated at 2 hours, 4 hours and 6 hours after the ECT procedure in the psychiatric ward. Rescue analgesic requirements, as well as, requirements side effects such as bradycardia (heart rate <60 beats per minute), hypotension (decrease in systolic arterial pressure of 20 mmHg from baseline), respiratory depression (respiratory rate <10), and nauseas and vomiting were also recorded. Patients with nausea and vomiting were given intravenous ondansetron 4mg.

Statistical analysis

We compared groups using ANOVA test of continuous variables with normal distribution and chi-square test for categorical data. We use a The P-value significance criteria < 0.05. IBM Statistics 17 was used for statistical analysis. The sample size was calculated according to a 0.45 incidence of 0.45 (14). As a result, 66 patient per group would provide 88% confidence level.

RESULTS

A total of 225 patients were included in the study and received acetaminophen, dexketoprofen trometamol or placebo over three week period. There were no differences on the demographic data, but the ECT duration was shorter in acetaminophen group (Table 1).

Table 1. Demographic data and ECT duration

| Variables                  | Acetaminophen (n= 75) | Dexketoprofen (n= 75) | Placebo (n= 75) | P Value |
|----------------------------|-----------------------|-----------------------|----------------|---------|
| Sex, male/female           | 39 (52)/36 (48)       | 33 (44)/42 (56)       | 35 (47)/40 (53) | 0.607   |
| Age, y.o                   | 34± 14                | 35 ± 14               | 36 ± 11        | 0.841   |
| Height, cm                 | 169 ± 12              | 168 ± 11              | 166 ± 7        | 0.112   |
| Weight, kg                 | 75 ± 13               | 71 ± 12               | 66 ± 13        | 0.000   |
| Psychiatric disorder       |                       |                       |                | 0.010   |
| - Depression               | 22 (29)               | 38 (51)               | 33 (44)        |         |
| - Obsessive Compulsive disorder | 14 (19)             | 19 (25)               | 13 (17)        |         |
| - Schizoaffective disorder | 39 (52)               | 18 (24)               | 29 (39)        |         |
| Duration of ECT, Sec       | 9 ± 15                | 11.1 ± 3.2            | 10.6 ± 2.8     | 0.000   |

Data expressed as number (%) or Mean ±SD, as appropriate.
The most common diagnosis in the study population was depression (41%), followed by schizoaffective disorder (38%), and obsessive compulsive disorder (21%). There were no differences between groups in the headache VAS scores at 2 and 4 hours after the procedure. However, patients who received dexketoprofen-trometamol have persistent headache at 6 hours after the procedure, compared to acetaminophen and placebo groups (Figure 1). Moreover, there were no differences between groups in the need of rescue analgesia at 2 and 6 hours after the procedure (chi-square test p = 0.235 and p = 0.366, respectively), with almost no requirements at 6 hours after the procedure. At the 4th hour, 11% of patients in placebo group requires rescue analgesia compared to none in the other two groups (p = 0.000) (Table 2).

There were differences between the groups in terms of HR, MAP and RR. Patients who received dexketoprofen had higher heart rate at 6 hour, whereas in participants who received acetaminophen MAP at 6th post-procedure was higher compared to the other two groups (p<0.005) (Table 2). Moreover, patients in placebo group had lower respiratory rate over the 6 post-procedure hours (p< 0.001, each). Finally, no incidence of adverse events was report

Table 2. Analgesic consumption and vital signs after ECT procedure Data expressed as number (%) or Mean ± SD, as appropriate.

| Variables                  | Acetaminophen (n=75) | Dexketoprofen (n=75) | Placebo (n=75) | P Value |
|----------------------------|----------------------|----------------------|----------------|---------|
| Analgesic Consumption      |                      |                      |                |         |
| 2nd hour                   | 5 (6.7)              | 2 (2.7)              | 7 (9.3)        | 0.235   |
| 4th hour                   | 0 (0%)               | 0 (0%)               | 8 (10.7)       | 0.000   |
| 6th hour                   | 1 (1.3%)             | 0 (0%)               | 0 (0%)         | 0.366   |
| Heart rate, bps            |                      |                      |                |         |
| 2nd hour                   | 94 ± 15              | 91 ± 13              | 94 ± 15        | 0.162   |
| 4th hour                   | 98 ± 15              | 94 ± 15              | 98 ± 14        | 0.119   |
| 6th hour                   | 96 ± 16              | 91 ± 13              | 97 ± 14        | 0.012   |
| Mean arterial pressure     |                      |                      |                |         |
| 2nd hour                   | 82 ± 9               | 81 ± 8               | 81 ± 9         | 0.687   |
| 4th hour                   | 82 ± 9               | 80 ± 7               | 80 ± 8         | 0.122   |
| 6th hour                   | 84 ± 10              | 79 ± 8               | 80 ± 7         | 0.002   |
| Respiratory rate           |                      |                      |                |         |
| 2nd hour                   | 13 ± 1               | 13 ± 1               | 12 ± 2         | 0.000   |
| 4th hour                   | 13 ± 1               | 12 ± 1               | 11 ± 2         | 0.000   |
| 6th hour                   | 12 ± 1               | 12 ± 1               | 11 ± 1         | 0.000   |

Figure 1. Boxplot of Visual Analogue Scale 2nd, 4th, 6th hours after ECT between acetaminophen, dexketoprofen trometamol and placebo group
DISCUSSION

In this single-center, double-blind study we assessed the efficacy of dexketoprofen and acetaminophen to reduce headache after ECT. The main findings showed that there are not difference among the use of acetaminophen, dexketoprofen or placebo as preemptive analgesic during the first 4 hours post-ECT headache. However, patients who received dexketoprofen have slightly higher pain scores than the other 2 groups at 6 hours after the procedure. Patients in the placebo group had the higher requirements of rescue analgesia at 4 hours post-ECT.

Our findings are similar with Isuru A. et al. who showed that, preemptive analgesia with acetaminophen decreases the incidence and severity of headache after ECT procedure compared to placebo in a cohort of 63 patients (3). However, there is a small difference in design that reflects in the results, demonstrated decrease at pain scores at 2 hours after the procedure while we found it at 4 hours. The explanation for this difference seems to be related to the timing of acetaminophen administration which was 2 hours before the ECT procedure while in our study it was administered 30 minutes before. Leung M et al. conducted a crossover study comparing ibuprofen vs placebo administered 90 minutes before the ECT. They found a significant reduction of VAS headache score in those patients who received ibuprofen compared to placebo (14). Nonetheless, a recent work by Karaaslan et al. did not find significant differences in the use of intravenous paracetamol or ibuprofen compared to placebo for the pretreatment of headache and myalgia during the next 24 hours after ECT (15). They attributed their conflicting findings to a small sample of patients (totally 60 patients, n=20 patients in each group) and features of psychiatric diseases.

Moreover, we found that patients in the placebo group required rescue analgesia while the ones on the other group did not. Previous studies reported a reduction in the requirements of ibuprofen when compared to placebo (47% vs. 88%) (14). The difference in the requirement of additional analgesics in the study conducted by Leung M et al. compared to our study may be related to the timing of the preemptive analgesia administered (90 vs. 30, respectively). Despite of this, the findings correlate in favor of preventive analgesia to reduce the need for additional use of analgesics after ECT.

The strengths of our study are the fact that it is a randomized trial and our groups have a good balance between them. The only differences were seen in weight and a small variation in the duration of ECT in the acetaminophen group requiring shorter period of time in comparison to dexketoprofen and placebo groups. This may be related to the increasing on endocannabinoids levels, associated to acetaminophen use, which in turn are potent anticonvulsants (16). Moreover, some patients may find difficult to measure the headache through self-reported scales and post-ictal status may influence their response of patients. Since pain is a subjective phenomenon, the clarity of VAS instructions plays a fundamental role in the outcomes. In consequence, we specifically trained our patients before the procedure. The biggest limitation is that clinical manuals of electroconvulsive therapy recommend motor seizure lasting 20-25 seconds to consider electroconvulsive therapy as therapeutic (17) and the patients tested in our study presented shorter periods of motor seizure. Therefore, a shorter motor seizure may impact in the intensity of headache experienced after ECT.

In summary, there were no difference among efficacy of dexketoprofen, acetaminophen and placebo to reduce headache in the postoperative six hours period after ECT. Therefore using preemptive analgesics to decrease post ECT headache is not justified.

Ethical approval

All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.
Declaration of competing interest
The authors declare that they have no conflict of interest.

Funding
The authors have no financial relationships relevant to this article to disclose.

REFERENCES

1. Shorter E. The history of ECT: unsolved mysteries. Psychiatric Times. 2004;21(2):93.
2. Cerletti U. Old and new information about electroshock. American Journal of Psychiatry. 1950;107(2):87-94.
3. Isuru A, Rodrigo A, Wijesinghe C, Edirweera D, Premadasa S, Wijesekara C, et al. A randomized, double-blind, placebo-controlled trial on the role of preemptive analgesia with acetaminophen [paracetamol] in reducing headache following electroconvulsive therapy [ECT]. BMC psychiatry. 2017;17(1):275.
4. Atagun MI, Yildirim MS, Canbek O. Electroconvulsive Therapy: An Update/Elektrokonvulzif Tedavi: Bir Güncellemeye. Psikiyatride Güncel Yaklaşımlar/Current Approaches to Psychiatry. 2012;4(3):350-71.
5. Sayar GH, Öztén E, Eryılmaz G, Gül IG, Ceylan ME. Elektrokonvulzif tedavi üzerine güncel bir gözden geçirme. Psikiyatride güncel yaklaşımlar. 2014;6(2).
6. Abrams R. Electroconvulsive therapy: Oxford University Press; 2002.
7. Munk-Olsen T, Laursen TM, Videbech P, Mortensen PB, Rosenberg R. All-cause mortality among recipients of electroconvulsive therapy: register-based cohort study. The British Journal of Psychiatry. 2007;190(5):435-9.
8. Drew B, King ML, Callahan L. Cryotherapy for treatment of ECT-induced headache. Journal of psychosocial nursing and mental health services. 2005;43(4):32-9.
9. Weiner SJ, Ward TN, Ravaris CL. Headache and electroconvulsive therapy. Headache: The Journal of Head and Face Pain. 1994;34(3):155-9.
10. Kramer BA, Kadar AG, Clark K. Use of the Neuro-Wrap system for severe post-electroconvulsive therapy headaches. The journal of ECT. 2008;24(2):152-5.
11. Dinwiddie SH, Huo D, Gottlieb O. The course of myalgia and headache after electroconvulsive therapy. The journal of ECT. 2010;26(2):116-20.
12. Khan S, Qayyum R, Buland K, Ujala M, Zubair UB. Role of perioperative analgesia with acetaminophen in reducing pain following electroconvulsive therapy. Pakistan Armed Forces Medical Journal. 2019;69(5):943-48.
13. Zippel H, Wagenitz A. Comparison of the efficacy and safety of intravenously administered dexketoprofen trometamol and ketoprofen in the management of pain after orthopaedic surgery. Clinical drug investigation. 2006;26(9):517-28.
14. Leung M, Hollander Y, Brown GR. Pretreatment with ibuprofen to prevent electroconvulsive therapy-induced headache. J Clin Psychiatry. 2003 May;64(5):551-3.
15. Karaaslan E, Akbas S, Ozkan AS, Zayman EP. Effects of preemptive intravenous paracetamol and ibuprofen on headache and myalgia in patients after electroconvulsive therapy: A placebo-controlled, double-blind, randomized clinical trial. Medicine (Baltimore). 2019 Dec;98(51):e18473. doi: 10.1097/MD.00000000000018473.
16. Deshpande LS, DeLorenzo RJ. Acetaminophen inhibits status epilepticus in cultured hippocampal neurons. Neuroreport. 2011;22(1):15–18. doi:10.1097/WNR.0b013e3283413231
17. Mankad MV, Beyer JL, Krystal A, Weiner RD. Clinical Manual of Electroconvulsive Therapy. Washington, DC: American Psychiatric Publishing, Inc.; 2010.