EFFICACY OF INTRAVENOUS KETOROLAC IN POST ELECTRO-CONVULSIVE THERAPY (ECT) HEADACHE

Muhammed Umer, Farrukh Saleem Shah*, Sajid Rahim**

Combined Military Hospital Jhelum Pakistan, *Pakistan Naval Ship Shifa, Karachi Pakistan, **Combined Military Hospital Bahawalpur/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To compare the mean headache score after single dose Intra-venous (I/V) ketorolac administered as part of General Anaesthesia (GA) following Electro-convulsive Therapy (ECT) versus placebo.
Study Design: Randomized controlled trial.
Place and Duration of Study: Psychiatry Department, CMH Lahore, from Jun 2014 to Dec 2014.
Methodology: 100 patients fulfilling the inclusion criteria were selected after permission from Hospital Ethical Committee and completion of informed written consent. Registration numbers, name, age and gender were noted. Patients were divided into two groups randomly by using random number table. In group A, Intravenous Ketorolac 0.5mg/kg body weight was given to all patients as part of medications administered at the time of ECT while in group B placebo (normal saline) was given. All patients were assessed 2 hrs after ECT for subjective experience of headache on Visual Analogue Scale (VAS). All the information was collected through well defined proforma.
Results: Headache scores showed significant improvement after treatment with a *p*-value <0.001. Mean score in placebo group was 4.54 ± 2.83 whereas the mean headache score in ketorolac group was 2.48 ± 2.34. Single dose I/V ketorolac reduced 2.06 ± 0.52 score in headache compared to placebo group. There was a statistically significant decrease in headache score after treatment.
Conclusion: Based on our results single dose I/V ketorolac is effective with respect to placebo in reducing post-ECT headache.

Keywords: General anaesthesia, Non-steroidal Anti-inflammatory drugs, Pain.

INTRODUCTION

Electro-Convulsive Therapy (ECT) is a safe and effective treatment commonly used for severe depression, catatonia and prolonged or severe mania even today in-spite of misinformation by media[1] and misconceptions in the minds of lay people, as well as, those related to medical profession[2]. It seems appropriate when there is a need for a rapid definitive response, as in suicidal patients or in hyperactive patients who may be a risk for themselves or others. The efficacy and safety of ECT has been demonstrated in various meta-analysis and systematic reviews[3-5].

However like other treatment modalities it is also associated with some adverse side effects. Immediately following ECT treatment the most common adverse effects reported by patients are headache, disorientation, and memory complaints[6,7]. Headache has been reported in up to 50% of patients[7]. The throbbing character of postECT headache suggests a similarity with vascular headache, and ECT may be associated with a temporary change in quality of headache from muscle-contraction type to vascular type. Although the exact etiology of post-ECT headache is unknown, there are several theories; Up-regulation and subsequent sensitization of 5-HT2 receptors may trigger a vascular type headache ECT results in direct stimulation of the masseter, temporalis, and pterygoid muscles which is not attenuated by administration of succinylcholine. The associated jaw clamping may produce headache and other theories suggest that increased cerebral blood flow and blood pressure during ECT may contribute to the onset of headache[8]. The American Psychiatric Association (APA)

Correspondence: Dr Muhammed Umer, Graded Psychiatrist, CMH Jhelum Pakistan (*Email: omer_364@yahoo.com*)
Received: 06 Apr 2017; revised received: 25 Nov 2018; accepted: 27 Dec 2018

suggests symptomatic treatment of post ECT headaches with aspirin, acetaminophen or non-steroidal anti-inflammatory medications includeing intravenous ketorolac[8]. The APA further suggests that patients who experience frequent post-ECT headache may benefit from symptomatic or prophylactic treatment with these medications[8]. Ketorolac is a non-steroidal anti-inflammatory drug providing relief from short-term acute pain. Patients who experience frequent post-ECT headache may benefit from prophylactic treatment, such as Aspirin, Acetaminophen[9], Ibuprofen[10] or Topiramate[11] given as soon as possible after ECT, or even immediately prior to the ECT treatment.

This study was carried out to validate the usefulness of I/V ketorolac as part of GA for post-ECT pain control in local population. The studies carried out on this topic were on an inadequate sample size i-e 10, 8 patients[9-12] and revealed controversial results. We intended to conduct this study on an adequate sample size i.e. 100 patients to generate reliable results.

METHODOLOGY

This randomized control trial was performed at Psychiatry department, CMH Lahore, from 12th June 2014 to 11th December 2014. Sample size was calculated using WHO calculator with confidence interval of 95% level of significance 5% and power of test is 90%[10]. A total number of 100 patients were enro-lled in the study from Psychiatry department, CMH Lahore. Patients undergoing ECT irres-pective of the type of psychiatric disorder, gender and aged 18-60 yrs were selected after permission from Hospital Ethical Committee and completion of informed written consent by non-probability consecutive sampling. Patients having previous history of headache (primary or other secondary causes of headache), non-consenting and allergic to ketorolac were excluded from the study.

Registration numbers, name, age and gender were noted. Fifty patients were distributed randomly in two groups (group A-ketorolac group and group B-placebo group) by using random number table.

In group A, Intravenous Ketorolac 0.5 mg/ kg body weight was given to all patients as part of medications administered at the time of ECT while in group B placebo (normal saline) was given. All patients were assessed 2 hrs after ECT for subjective experience of headache through well defined proforma of Visual Analogue Scale (VAS) (attached as Annex lll). VAS is an 11 point scale used for measuring self-reported headache in this study and ranged from score of 0 (being no pain at all) to 10 (being the worst pain).

Data analysis was computer based with the use of SPSS version 19. Mean and standard deviation was calculated for headache score and age in both groups. Since headache is an ordinal variable, Mann Whitney U-test was used to determine the significant difference in both groups for mean headache score. *p*-value ≤0.05 was taken as significant. Effect modifiers such as age and gender were controlled by stratification and then post-stratification chi-square test and mann–whitney U-test were applied.

RESULTS

A total number of 100 patients were enrolled in the study from Psychiatry department, CMH Lahore. These patients were distributed randomly in two groups (group A-ketorolac group and group B-placebo group), 50 patients in each group. The distribution of headache score in each group is shown in figure. There were 83 (83%) males and 17 (17%) females in the study sample. The mean age of the females was 35.35 ± 9.52 years and the mean age for males was 38.77 ± 11.08 years. The mean age of the patients was 38.19 ± 10.87 years with minimum age of 19 and maximum age of 59 years. Mean age of the patients in ketorolac group was 37.86 ± 10.99 yrs and mean age in placebo group was 38.52 ± 83 yrs. On applying Kolmogrov-Smirnov Test to test the normality of the headache score data, it was found out that the data was not normally distributed (p<0.001). The mean headache score for the group A (2.48 ± 2.34) was found to be

significantly less than the mean headache score for group B (4.54 ± 2.8) with $p<0.01$ (table-I). Gender was not an effect modifier for the headache score (table-II, & III) whereas age was not an effect modifier for headache score (tables-IV & V respectively). Twenty five (25%) patients report no headache. In group A 15 (30%) and in group B 10 (20%) patients reported no headache.

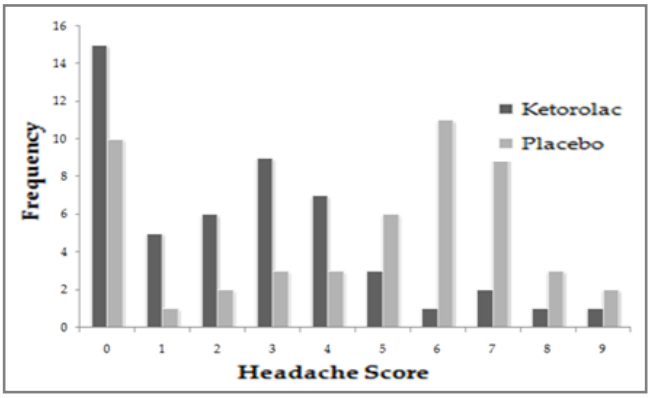

Figure: Frequency distribution of headache scores (n=100).

DISCUSSION

Electroconvulsive Therapy is being used to treat various psychiatric disorders for decades. It is not a popular form of treatment as there are various reasons; side effects profile and negative media connotation are amongst the few. Advances in GA have greatly reduced the post ECT side effects but headache is still reported in up to 50% of the patients[7].

We planned this study considering the fact that ECT was being performed increasingly locally and to compare the improvement in headache with ketorolac. The advantage of ketorolac over other symptomatic treatments is its availability in intravenous form as compared to other drugs and can be given as part of general anaesthesia. The study was funded by the Department of Psychiatry, CMH Lahore.

In our study, out of 100 cases (50 in each group) some patients reported no headache (group-A 15 (30%) and group-B 10 (20%)). This is also consistent with findings of previous studies that headache is reported in 50% of the patients only[8]. However greater number of patients in group-A may represents those patients who had mild headache and were relieved by its administration but it needs to be studied independently.

The findings of the study are in agreement with previous studies that prophylactic treatment of headache results in better post ECT relief of headache[9-12,14-15]. Intravenous Ketorolac reduces headache effectively in patients experiencing headache after ECT. Since exact etiology of headache is not known, Markowitz *et al* in open label trial measured post ECT headache and treated it with intranasal sumatriptan (considering the vasodilatation theory) and achieved similar results. The headache score was significantly reduced (p-value=0.002) at 0.5, 1, 1.5, and 2 hours when compared with baseline[15-18]. This shows that different drugs with different modes of action can also be combined to reduce severe

Table-I: Mean headache score in each group.

Group Statistics				
	Group	**n**	**Mean ± SD**	***p*-value**
Headache Score	Ketorolac	50	2.48 ± 2.341	<0.001
	Placebo	50	4.54 ± 2.837	

Table-II: Mean headache scores for groups A and B as per gender (n=100).

	Ketorolac	**Placebo**
Males	2.57 ± 2.82	4.45 ± 2.95
Females	2.47 ± 2.29	4.90 ± 2.42
p-value	0.93	0.65

Table-III: Frequency distribution of groups A and B as per gender (n=100).

	Ketorolac	**Placebo**	**Total**	***p*-value**
Males	43	40	83	0.42
Females	7	10	17	
Total	50	50	100	

Table-IV: Mean headache scores for groups A and B as per age groups (n=100).

	Ketorolac	**Placebo**
18-35 Years	2.04 ± 2.21	3.50 ± 2.97
36-60 Years	2.92 ± 2.43	5.36 ± 2.48
p-value	0.19	0.02

Table-V: Frequency distribution of groups A and B as per age groups (n=100).

Years	**Ketorolac**	**Placebo**	**Total**	***p*-value**
18-35	25	22	47	0.55
36-60	25	28	53	
Total	50	50	100	

headache but this need to be studied independently.

The results of our study with the support of the above studies are justifying the hypothesis that "There is a difference in mean headache score after single dose of I/V ketorolac versus placebo following ECT. The results of this study may be applied to patients reporting headache after ECT.

LIMITATION OF STUDY

Twenty Five (25%) patients reported no headache. Patients reporting no headache in each group were, group-A 15 (30%) and group-B 10 (20%). This could possibly create a bias in measuring means of every group. This bias can be removed by selecting only those patients who report headache after ECT and measure the headache score in the same group before and after ketorolac intervention.

CONCLUSION

Our study has confirmed that single dose I/V ketorolac is effective with respect to placebo in reducing post-ECT headache. This protocol can not only benefit the patients by reducing their post ECT-headache and also help in promoting the ECT as a safe procedure. Our intent was to use simple treatment which is easy to administer and cost effective.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. National Institute for Health and Clinical Excellence 2011. The clinical effectiveness and cost effectiveness of electroconvulsive Therapy (ECT) for depressive illness, schizophrenia, catatonia and mania. Clinical Guidance TA59. Available on: http://www.nice.org.uk/TA059
2. Khan FH, Khan KH. Electro convulsive therapy; generally ignored but still an effective treatment modality. Professional Med J 2006; 13(4): 481-87.
3. Dierckx B, Heijnen WT, van den Broek WW, Birkenhäger TK. Efficacy of electroconvulsive therapy in bipolar versus unipolar major depression: A meta-analysis. Bipolar Disord 2012; 14(2): 146-50.
4. UK ECT Review Group. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. Lancet 2003; 361(9360): 799-808.
5. Pagnin D, de Queiroz V, Stefano Pini, Cassano GB. Efficacy of ECT in Depression: A Meta-Analytic Review FOCUS. J ECT 2008; 6(1): 155-62.
6. Hamdani A, Farjam A, Jehangir S. Effects of electro convulsive therapy on cognitive functions in patients of depressive episode. Pak Armed Forces Med J 2007; 57(4): 279-85.
7. Devanand DP, Fitzsimons L, Prudic J, Sackeim HA. Subjective side effects during electroconvulsive therapy. Convuls Ther 1995; 11(4): 232-40.
8. American Psychiatric Association. The practice of ECT: Recommendations for treatment, training, and privileging. American Psychiatric Press Inc., Washington DC. 2001.
9. Kertesz DP, Trabekin O, Vanetik MS. Headache treatment after electroconvulsive treatment: A single-blinded trial comparator between eletriptan and paracetamol. J Extra Corporeal Technol 2015; 31(2): 105-109.
10. Leung M, Hollander Y, Brown GR. Pre-treatment with ibuprofen to prevent electroconvulsive therapy-induced headache. J Clin Psychiatr 2003; 64(5): 551-53.
11. Ye L, Karlapati SK, Lippmann S. Topiramate for Post-Electroconvulsive therapy headaches. J ECT 2013; 29(3): e49.
12. GR Keith. A randomized control trial of ketorolac for prevention of headache related to electroconvulsive therapy. Pacific Standard Time 2013; 1(2): 5-8.
13. Raymond W, McIntosh D, Wang J, Murray W, Kolivakis T, Erin E, et al. Canadian Psychiatric Association, Canadian Network for Mood and Anxiety Treatments (CANMAT). Clinical guidelines for the treatment of depressive disorders. Can J Psychiatr 2001; 46(Suppl-1): S5-10.
14. DeBattista C. Sumatriptan prophylaxis for post ecletro-convulsove therapy headache. Headache 1995; 35(8): 502-03.
15. Markowitz JS, Kellner CH, DeVane CL, Beale MD, Folk J, Burns C, et al. Intranasal sumatriptan in post-ECT headache: results of an open-label trial. J Extra Corporeal Technol 2001; 17(4): 280-83.
16. Leung M, Hollander Y, Brown GR. Pretreatment with ibuprofen to prevent electroconvulsive therapy-induced headache. J Clin Psy 2003; 64(5): 551-53.
17. Genz A, Krause P, Koch RD, Knorr W. Side effects of bilateral electroconvulsive therapy - comparative clinico-computer tomographic study. Psychiatr, Neurol, Medizinische Psychol, 1985; 37(4): 197-204.
18. Fantz RM, Markowitz JS, Kellner CH. Sumatriptan for post-ECT headache. J ECT 1998; 14(4): 272-74.