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Improving the effectiveness of electroconvulsive therapy through the determination of anaesthetic depth. Preliminary results☆

Mejora de la efectividad de la terapia electroconvulsiva mediante la determinación de la profundidad anestésica. Resultados preliminares

Dear Editor,

The anaesthetic agents such as propofol used in modified ECT may hinder an optimum convulsion[1], thereby reducing its antidepressant effect and increasing the secondary cognitive effects because the stimulus energy has to be increased[1]. The PSI (Patient State Index) was specifically designed to control patient sedation and the effect of drugs in intraoperative interventions and intensive cures[2], predicting loss of consciousness and detecting intraoperative waking[3]. Use of this index has made it possible to reduce the dose of propofol used in anaesthesia, improving recovery time without increasing intraoperative recall[4]. The first results are presented of an experimental prospective study with a control group, to determine the impact in terms of efficacy and safety of using the ECT procedure while monitoring the depth of anaesthesia using the PSI, in comparison with the traditional clinical method.

The sample is composed of 31 patients admitted to the BM-CASM-HGG Psychiatric Unit. They were recruited from November 2017 to September 2020 and fulfilled the criteria for major depressive disorder according to the DSM-IV-TR and the indication for ECT.

This study fulfils the conditions of the Helsinki Declaration, and it was approved by the Clinical Research Ethics Committee of Granollers H. General. The patients voluntarily accepted taking part, giving their informed consent. 2 sessions per week with propofol and succinylcholine took place, using Thymatron SYSTEM IV apparatus (Somatics LLC, U.S.A.), and determining the PSI with a SedLine® monitor (Masimo Corporation, U.S.A.). The stimulus dose was calculated using the ''age-based method''[5] and using a pulse width of 0.5 ms. for bifrontotemporal ECT and 0.25 ms. for the unilateral right side. Patients in the PSI group were stimulated when its value showed a tendency to rise between the values of 50–70, and those in the control group were stimulated when the score was 5–6 on the Ramsay scale[6] and the fasciculations caused by the succinylcholine had ended. Patients were re-stimulated if the convulsion lasted for less than 25 s in the EEG. The appropriateness of the convulsion was evaluated in each session according to a method similar to that used by Rattehalli[7], together with the presence of delirium and waking intra-ECT[8]; likewise clinical state using HDRS-17 and CGI in alternating sessions and cognitive state with the MCE. The patients finalized the study when they achieved clinical remission or if after 12 sessions this was not possible, and if with a stimulus of 100% energy a convulsion of at least 25 s was not achieved.

The SPSS program (version 23, IBM Corp., NY, U.S.A) was used for statistical analysis; the Mann-Whitney U test was used for quantitative variables and the χ^2 test was used for qualitative variables. Statistical significance was considered to exist if $P \leq .05$.

No statistically significant differences were found between the clinical and sociodemographic characteristics of both groups. The average PSI value was 56.71 ± 6.81.

The PSI group obtained longer and higher quality convulsions with less energy, and required fewer repeat stimulations (Table 1). Unlike other studies[9], the number of sessions was neither lower nor statistically significant in the PSI group, probably because of the small size of the sample. The use of repeat stimulations and higher stimulation energies have been associated with adverse cognitive effects[10], and although we did not find this, it is possible that more sensitive tests than the MCE would be required[11].

The waiting time until the ideal PSI value was reached may explain reduced action of the anaesthesia at the instant of stimulation, as other studies have shown[12], and that in

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Table 1 Results in terms of efficacy and safety.

	PSI-TEC	TEC	Statistical analysis	
			Test	*p*
No. of sessions, average (SD)	6.64 (3.71)	6.59 (3.64)	Mann-Whitney *U* test = 115	0.87
Repeat stimulation, *n* (%)	5 (2.7)	43 (19.2)	$\chi^2 = 26.61$ gl = 1	<0.001
No convulsion with E = 100%, *n* (%)	0	3 (17.6)	Fisher's exact test	0.23
Dose of propofol mg/session, average (SD)	77.6 (22.9)	70.1 (21.6)	Mann-Whitney *U* test = 4225.5	0.019
Dose of propofol mg/kg, average (SD)	1.2 (0.39)	1.1 (0.34)	Mann-Whitney *U* test = 4195.5	0.017
Stimulus energy Mc, average (SD)	232.16 (126.6)	258.05 (107.6)	Mann-Whitney *U* test = 5828	0.022
Convulsion duration EEG in sec., average (SD)	39.95 (14.2)	34.6 (20.8)	Mann-Whitney *U* test = 5374	0.001
Suitable convulsion, *n* (%)	71 (75.5)	60 (39)	$\chi^2 = 31.33$ gl = 1	<0.001
Waking time in sec., average (SD)	473.1 (179.4)	558.11 (225.22)	Mann-Whitney *U* test = 3505.5	0.004
Delirium (CAM), *n* (%)	1 (1.2)	2 (1.8)	Fisher's exact test	1
Intra-ECT waking, *n* (%)	0	3 (3.2)	Fisher's exact test	0.25
HDRS-17 final, average (SD)	8.29 (4.91)	8.88 (5.58)	Mann-Whitney *U* test = 102.5	0.51
CGI final $\leq$4, *n* (%)	12 (46.2)	14 (53.8)	Fisher's exact test	1
GAF final, average (SD)	64.36 (9.25)	62.88 (11.28)	Mann-Whitney *U* test = 108.5	0.88
Final MCE, average (SD)	29.77 (5.54)	29.35 (4.73)	Mann-Whitney *U* test = 97.5	0.58

CAM: Confusion Assessment Method; CGI: Clinical Global Impression; EEG: electroencephalogram; GAF: Global Assessment of Functioning; HDRS-17, Hamilton Depression Rating Scale-17; MCE: Mini Cognitive Exam.

this group effectiveness improved in spite of the patients receiving a higher dose of propofol. The higher dose may be due to occasional supplementation to optimize sedation during the said waiting time.

Using the PSI maintains the efficacy of the procedure, as it achieves a level of remission comparable to the group treated traditionally.

No patient in the PSI group mentioned intra-ECT recall, although the possible presence of anterograde amnesia at the moment of evaluation may have influenced this.

The size of the sample, the lack of double blind and non-standardization of PSI values in a psychiatric population are limitations that should be taken into account.

We believe this to be the first study in which the PSI is applied in ECT, and it may be concluded that it is a suitable means of determining when to apply the stimulus. It improves the efficacy of the latter, giving better convulsions with less stimulus energy and fewer repeat stimulations). It does not affect safety, without any greater cognitive affect or increased intra-ECT awareness, although this requires confirmation in larger samples.

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Conflict of interests

The authors have no conflict of interests to declare.

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Another Godot who is still not coming: More on biomarkers for depression☆

Otro Godot que todavía no viene: más sobre los biomarcadores de depresión

Dear Editor,

The July 2021 Editorial inspired us to add another ''Godot'' to the list. As the Author pointed out[1] – *changing clinical guidelines in the traditionally biomarker-aversive field of psychiatry is not an easy step*-indeed. That so well applies to depression research, too.

The knowledge from decades-long research in complex systems dynamics offers tools for extracting information from electrophysiological signals (ECG, EEG, etc.). These tools provide high accuracy of detection of irregularities by quantifying subtle changes in signal patterns, using nonlinear measures, like different forms of statistical entropy (Shannon entropy, approximate entropy, sample entropy, multiscale entropy, etc.) or fractal dimension measures (Higuchi fractal dimension, detrended fluctuation analysis-DFA). Nonlinear parameters, like different forms of statistical entropy or fractal measures, calculated from electrophysiological signals (e.g., EEG or ECG), are demonstrated to be predictive of many psychiatric disorders and their phases. Beside diagnostics, complex system analysis can be used for monitoring therapy results (or forecasting responders to medication or other modalities of therapy like repetitive transcranial magnetic stimulation). Based on this analytic approach it is possible not only to accurately confirm depression, but also delineate between phases of disease (episode vs remission, like in[2]), differentiate between subtypes (melancholic vs non-melancholic depression), comorbidities, or even detect existing suicide risk.[3] Knowing those additional information early in the process can help in effectively choosing the therapy that increases the probability that the patient would recover and avoid relapses. Pincus[4] stresses the importance of *dynamics* of the systems, which requires a quantifier that is sensitive to the order of events in time series, for example, approximate entropy (ApEn). There is a lot of research demonstrating that nonlinear measures are much more accurate and reliable than the conventional ones in analyzing history sensitive systems.[5] Widely used Fourier transform that is embedded in any software in any operating machine made to record electrophysiological signals, is proven to be redundant to fractal analysis[6] and it is known to be not sensitive to detect early changes in the signal unlike other fractal and nonlinear methods.[7]

Perhaps especially urgent is detecting cardiovascular diseases (CVD) in people suffering from depression. The connection between these two diseases that carries a high mortality risk[8] has long been known[9] and yet monitoring heart function in depressive patients is far from clinical routine. The data can be easily obtained by novel portable ECG monitoring devices that are approved as medical-grade signal quality equivalent to holter, but are much more practical and comfortable to use by the patient her-/himself, leading to early detection of risks and potentially to personalized medicine at its very best. The data can then be processed by a combination of nonlinear analytics and advanced statistical procedures (to control, for example, for comorbidities, subtypes and other confounding factors[10]). Even better, the analysis can be empowered with machine learning applications[11] that are widely in use due to high power of computation and cloud computing.

This process is neither costly nor invasive, so, why wait to save lives?

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