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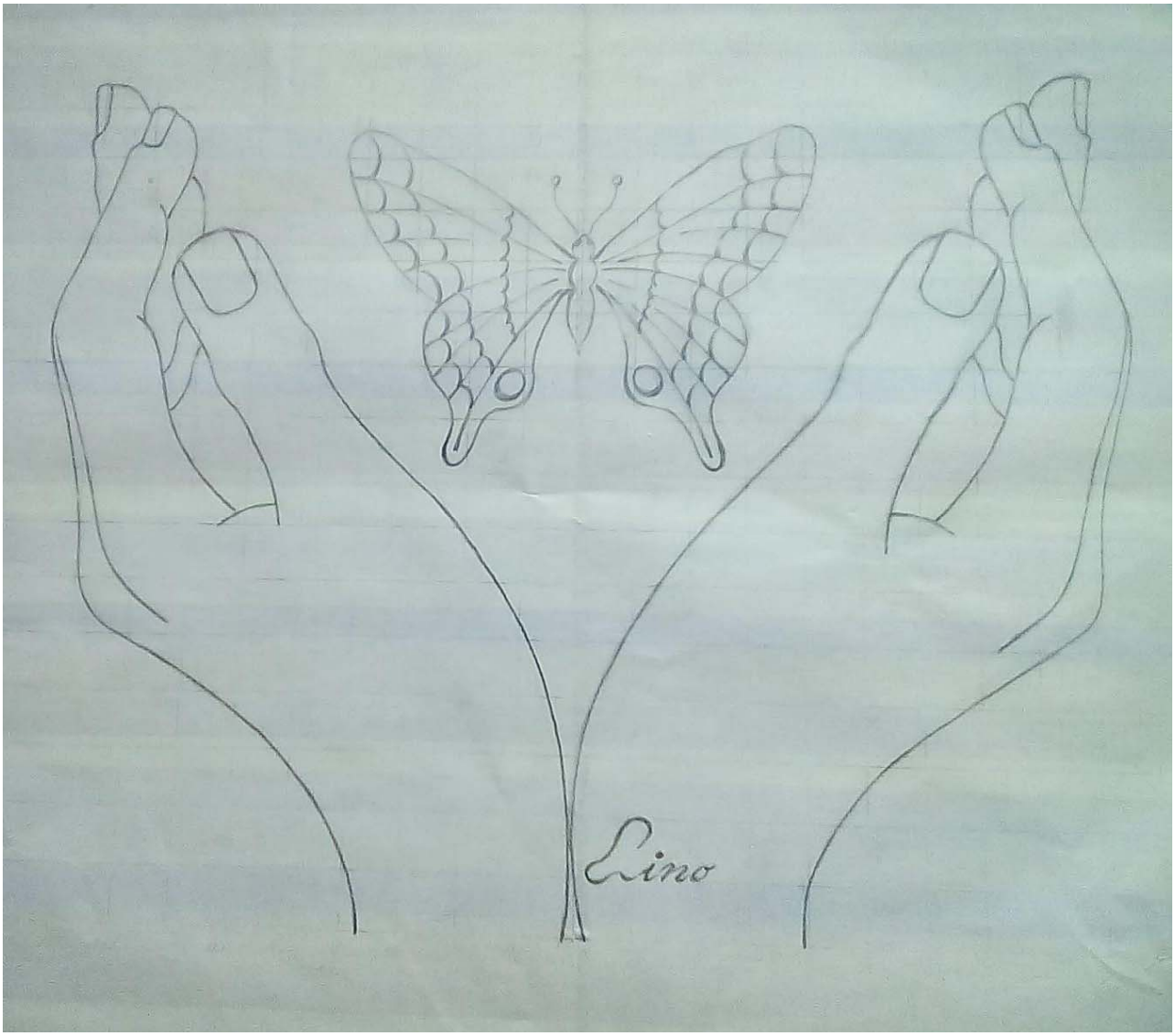

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Med – Inf SCIENTIFIC ASSOCIATION :

Organizational secretariat

Largo Cesare Beccaria n° 4; 04022 Fondi (Latina), Italy.

Tel. +39 333-3019781

E-mail: segreteria@med-inf.com

Role of Choline Alphoscerate (Gliatilin^{R}) in elderly patients.

*** Marchitto N., ** Paparello P.T., ** Pacella C., *** Coco I.,*** Piazza R., * Paradiso A., *Raimondi G.,**

*** "Sapienza" University of Rome "Polo Pontino"; ** Med-Inf Association, Fondi (Latina), Italy;**

***** Italfarmaco S.p.a. Medical Affairs Department, Milan, Italy.**

Corresponding Authors: Marchitto N. e-mail: **nicola.marchitto@uniroma1.it**

KEYWORDS: Cognitive impairment, MMSE, Choline Alphoscerate, Cardiovascular risk.

ABSTRACT

Background: Some drugs used in the treatment of cognitive impairment increase the risk of arrhythmia. International literature reports that the Heart Rate Variability (HRV), QT, Qtc and Tpeak-to-Tend indices are used in the clinical setting, as well as in scientific research, for arrhythmic risk stratification. **Methods:** The present study was designed to investigate the role of choline alphoscerate in cognitive impairment in terms of safety and efficacy Due to the advanced age of the patients and the difficulties in connecting with the Geriatric Department of the San Giovanni di Dio Hospital in Fondi, Latina, caused by the Sars-Cov2 pandemic, 120 patients (50 males and 70 females, average age 80 ± 7 years) suffering from cognitive impairment (average MMSE 18/30 ± 4), have been enrolled. During the enrollment period, patients underwent non-invasive electrocardiographic recording, in order to evaluate the effect on the autonomic nervous system using HRV evaluation and the safety of choline alphoscerate in relation to the cardiovascular risk explored by the analysis of QT, Qtc and Tpeak to T end Index (Tp/Te). The proposed treatment was choline alphoscerate (Gliatilin^{R}) in 600 mg capsules in two daily doses, for 3 months. Data were measured with the cardiolab xai-medica software and analyzed using SigmaStat 3.5 software for Windows. **Results:** A statistically significant improvement of the MMSE value (18,692 vs 21,077 with $P < 0,001$*) was observed after 1 month and a similar statistically significant improvement of the MMSE value (19,714 vs 19,905 with $P = 0,047$*) was observed after 3 months of the treatment with choline alphoscerate. No significant differences after 1 month in HRV explored in the time domain, in the

frequencies domain, with non-linear analyses, using arrhythmic index as QT interval and Tpeak to Tend index were observed. **Conclusion:** A statistically significant improvement of the MMSE value was observed after 30 days and after 90 days of the treatment. A reduction of the ortho sympathetic tone and a simultaneous hyperactivity of the parasympathetic tone with a cardioprotective effect, have been observed with Gliatilin^{R,} but the variation in autonomic indices does not underline a statistical significance.

key points

- **Efficacy:** Recent scientific articles in the literature highlight the effectiveness of treatment with choline alphoscherate (Gliatilin^{R}) (1) in patients suffering from cognitive impairment (2).
- **Safety:** In elderly patients, the concomitant administration of drugs may increase the risk of arrhythmias (9). Some drugs used in the treatment of cognitive impairment increase the risk of arrhythmia, especially when used in high doses to control behavioral disorders (8).

why does this paper matter? Cognitive impairment represents an increasingly emerging clinical condition in relation to the average lifespan of the population (3). The risk of arrhythmias is higher in the elderly population on poly pharmacological treatment (9). Therefore, it is necessary to propose effective and safe pharmacological treatments subjected to arrhythmia risk assessment based on scientific evidence (4).

INTRODUCTION

Contest

Wilhelm Lexis, in the 19th century, created a method of graphic representation to highlight the distribution of demographic events, reported on a Cartesian axis, as a function of the time represented on the abscissae and the age represented on the ordinate (Fig. 1). The analysis of the current Lexis pyramids allows us to extrapolate the modification characterized by the narrowing of the base linked to the low birth rate and the transformation of the pyramid into a trapezoidal figure due to the progressive increase in the elderly population and the progressive reduction in the birth rate (contracting phase of population growth). (Fig. 1-2).

Dementia represents an increasingly emerging clinical condition in relation to the lengthening of the average lifespan of the population (Fig.2). A systematic review of the literature relating to the treatment of cognitive impairment, highlights the pro-arrhythmic role of some pharmacological treatments that require careful and frequent electrocardiographic follow-up (5). The international literature provides different indices for the evaluation of arrhythmia risk. The HRV analyses (10), QT, Qtc and Tpeak-to-Tend indices are used in the clinical setting, as well as in scientific research, for arrhythmia risk stratification (Tab. 1). It is necessary to approach effective and safe pharmacological treatments. Safety and effectiveness data relating to choline alphoscerate (Gliatilin^{R}) in cognitive impairment have been reported in recent studies (6).

Aim: the present study aims to investigate the role of choline alphoscerate (Gliatilin^{R}) in cognitive impairment in terms of safety (Tab. 1) and efficacy (Tab. 2).

Objective

The objective of this study is to evaluate the effect of choline alphoscerate (Gliatilin^{R}) by

Mini Mental State Examination (MMSE) after 30 days and after 90 days of treatment (Tab. 2), and the safety of the treatment explored by heart rate variability (HRV) assessment to evaluate the autonomic nervous system balance (10), and the modification of the arrhythmic indices in basal conditions, after 30 days of treatment with Gliatilin^{R} (Tab. 1).

METHODS

– Participants and ethical approval

In July 2021, an observational study regarding the safety of treatment for cognitive impairment was carried out at the Department of General Medicine and at the Geriatric Clinic of the San Giovanni di Dio Hospital in Fondi, Latina (Italy). The proposed treatment is approved and available at local pharmacies, therefore only informed consent was requested for the processing of sensitive data and for non-invasive electrocardiographic measurements, carried out in baseline conditions and after pharmacological treatment with choline alphoscerate. Enrollment in the study was voluntary. Patients and caregivers were given informed consent which explains in detail the rationale for the study, the methods by which it was conducted and the possibility of interrupting the study at any time. Sensitive data were processed in compliance with privacy legislation. The pilot study began in July 2021 and was carried out by collecting and processing data from patients at the Geriatric Clinic of the San Giovanni di Dio Hospital, Fondi (Latina). The data from the study are related to 120 patients (70 men and 50 women) suffering from Dementia (with MMSE 18$\pm$4) and with an average age of 80$\pm$7 years.

– Data collection

All patients enrolled in the study provided their informed consent to the observational study. All patients continued home pharmacological treatments in respect with the ethical guidelines. As regards the use of scale, it has been standardized to the international reference system for laboratory tests and instrumental tests (7). Screening eligibility requirements included the age of at least 18 years old. All patients provided written informed consent for data collection. All patients enrolled in the study provided their informed consent to the observational study.

– Inclusion and exclusion criteria

The inclusion criteria consider the presence of cognitive impairment evaluated with Mini Mental State Examination (MMSE) and age over 65 years old. The inclusion criteria required for enrolment is represented by a MMSE value 18/30$\pm$4, in patients with Mild Cognitive Impairment. The exclusion criteria are attributable to the HRV analysis technique which does not allow to consider patients with rhythm abnormalities or atrial fibrillation. Therefore, the exclusion criteria included treatment with anti-arrhythmic drugs and the presence of

Implantable Cardiac Device (ICD) for the possible interference with the heart rate variability in heart disease patients, and to avoid distortions in the evaluation of the neuro-vegetative tone modulation. Patients with difficulties due to functional limitations, with inability to come to hospital for follow-up, are not included in the study.

– **Principal exposure variables**

The study was designed to evaluate the cognitive function using the standardized Mini Mental State Examination (MMSE) test (Tab. 2). To assess the arrhythmic risk, a digital electrocardiographic recording lasting 3 minutes or at least 250 heartbeats was performed. Using the analyses of the variations in the RR interval of the digital electrocardiogram in time domain (SDNN, RMSSD), in the frequencies domain (LF, HF, LF/HF), with non linear analyses (DFA alpha-1, DFA alpha-2, SD1, SD2, approximate entropy, sample entropy, Shannon entropy) (10), it was possible to extrapolate the data relating to the ortho sympathetic (LF) and parasympathetic (HF) autonomic nervous system (Tab. 1). From the analysis of the QT interval and the Tpeak to T end index, it was possible to evaluate the arrhythmic risk before and after pharmacological treatment with choline alphoscerate (Tab. 1). As regards the use of scale, it has been standardized to the international reference system for laboratory tests and instrumental tests.

– **Covariates**

Treatment with antiarrhythmic drugs can alter the electrocardiographic evaluation of heart rate variability (HRV) and arrhythmic indices in patients suffering from chronic heart disease, therefore the electrocardiographic recordings were carried out maintaining essential home treatment, without further increases in dosage, in order to avoid distortions of the heart rate variability and the values of the arrhythmic indices QT and Tpeak to Tend.

– **Outcomes**

Confirmation of the effectiveness of treatment with choline alphoscerate (Gliatilin^{R}) (2) (Tab. 2) and absence of neuro-vegetative side effects using HRV evaluation (10), or a QT index increase greater than 450 msec in men and 480 msec in women (Tab. 1).

– **Study design**

The design of the study was aimed at analysing cognitive function using the standardized Mini Mental State Examination (MMSE) test. To assess arrhythmic risk, a non-invasive digital electrocardiographic recording during about 3 minutes (or 250 heart beats) was performed. Computerized mathematical calculation, based on the fast Fourier transform formula, regressive analysis and nonlinear analyses of changes in the RR interval of the electrocardiogram, was used to extrapolate data relating to the ortho-sympathetic (LF) and para-sympathetic (HF) autonomic nervous system. From the measurement of the HRV (10), QT interval and

the Tpeak to T end index, it was possible to evaluate the arrhythmic risk before and after pharmacological treatment with choline alphoscerate. At the time of enrollment, a run-in period occurred to undergo all enrolled patients to non-invasive 12-lead digital electrocardiographic recording, in order to evaluate the effect of choline alphoscerate on cardiovascular risk, explored by the analysis of HRV in time domain (SDNN, RMSSD), in the frequencies domain (LF, HF, LF/HF), with non linear analyses (DFA alpha-1, DFA alpha-2, SD1, SD2, approximate entropy, sample entropy, Shannon entropy) (10), QT, Qtc and Tpeak to T end Index (Tp/Te). The three different cardiovascular risk indices were evaluated by electrocardiographic trace in the basal condition (T0) and after 30 days (T1) of the treatment with choline alphoscerate (Gliatilin^{R}) (Tab. 1). The treatment is performed using 600 mg caps in two daily administrations, for 30 days. To compare data about MMSE we have performed the treatment for 90 days of follow-up period (Tab. 2).

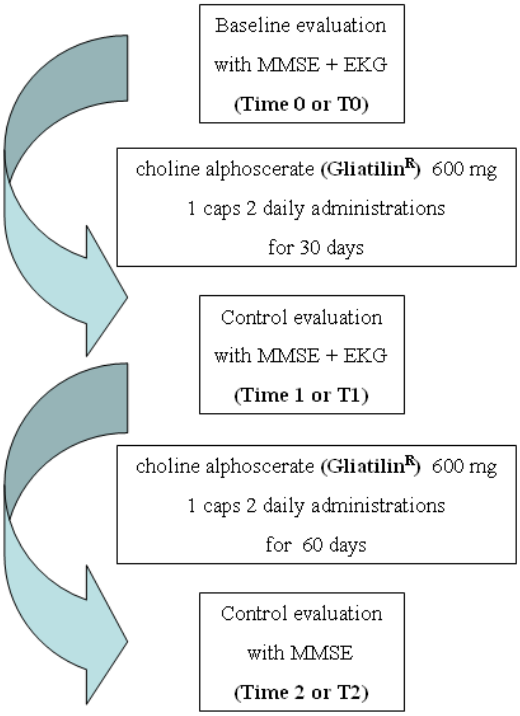
- **Statistical analysis**

Data was measured using cardiolab Xai-medica software, and analyzed with SigmaStat 3.5 software for Windows XP. Paired T test and ANOVA test were used to analyse the pre and post treatment data, recorded in the same subjects enrolled in the study. The Paired T test allows to perform comparative statistical analysis in small groups (Tab. 1). The ANOVA test (Tab. 2) is used to perform comparative statistical analysis on the same group in the three different periods (0-30-90 days). Statistical significance was fixed at $P < 0.05$.

RESULTS

- **study flow chart**

Baseline evaluation with MMSE + EKG (T0) => treatment with choline alphoscerate (Gliatilin^{R}) 600 mg caps in 2 daily administrations => Control evaluation after 30 days using MMSE + EKG (T1). Treatment with choline alphoscerate (Gliatilin^{R}) for 90 days and follow-up control using only the MMSE evaluation (T2).



Flow chart: Graphic representation of the study design.

- **baseline characteristics**

The mean age of the 120 patients enrolled was 80 ± 8 years. The group of patients that completed the follow-up period consisted of 50 men and 70 women. All enrolled patients have an elevated cardiovascular risk profile and a normal blood pressure (with their home pharmacological treatment). From July 2020 a total of 120 patients entered the run-in period. All patient's data respect the criteria for the study. No patients were randomized in error or were enrolled in violations of good clinical practice. Most patients received recommended drug therapy for chronic hypertension.

- **Primary Outcomes**

The primary outcome was the evaluation of the therapeutic effect of choline alphoscerate (2) at a dosage of 600 mg orally administered twice a day, using standardized cognitive test (MMSE) (5). Statistical analysis underline MMSE 18,692 ± 3,881 vs 21,077 ± 4,010 (with P < 0,001*****) after 30 days of treatment (Tab. 1) and MMSE value (19,714 ± 5,693 vs 19,905 ± 6,449 (with P = 0,047*****) after 90 days of treatment with choline alphoscerate (Gliatilin**R**) (Tab. 2).

- **Secondary outcomes**

The secondary outcome was the evaluation of the changes in the main pro-arrhythmic electrocardiographic indices like HRV explored in time domain (SDNN, RMSSD), in the frequencies domain (LF, HF, LF/HF), with non linear analyses (DFA alpha-1, DFA alpha-2, SD1, SD2, approximate entropy, sample entropy, Shannon entropy) (10) QT, QTc and Tp/Te after treatment with choline alphoscerate at a dosage of 600 mg orally administered twice a day. Statistical analysis underline no significative modification, after 30 days of treatment, about HRV explored in the time domain: SDNN 17,375 ± 10,715 vs 22,235 ± 27,631 (with P = 0,327); RMSSD 13,910 ± 6,373 vs 23,385 ± 41,318 (with P = 0,295); explored in the frequencies domain LF 61,580 ± 23,138 vs 61,360 ± 22,201 (with P = 0,972); HF 38,320 ± 23,095 vs 38,500 ± 22,138 (with P = 0,974); LF/HF 2,929 ± 3,047 vs 2,804 ± 2,583 (with P = 0,889); explored with non-linear analyses DFA alpha-1 1,077 ± 0,344 vs 1,069 ± 0,287 (with P = 0,919); DFA alpha-2 0,497 ± 0,187 vs 0,497 ± 0,196 (with P = 0,982); SD1 9,850 ± 4,519 vs 16,570 ± 29,275 (with P = 0,295); SD2 22,150 ± 14,859 vs 25,930 ± 26,719 (with P = 0,372); Approximate Entropy 1,006 ± 0,163 vs 1,030 ± 0,138 (with P = 0,417); Sample Entropy 1,546 ± 0,381 vs 1,649 ± 0,485 (with P = 0,339); Shannon Entropy 3,091 ± 0,358 vs 2,954 ± 0,582 (with P = 0,253) (10); arrhythmic index QT interval (msec) 387,700 ± 33,545 vs 398,350 ± 31,423 (with P < 0,132) QTc BAZZET (sec) 0,430 + 0,021 vs 0,447 + 0,048 (with P = 0,11), QTc FREDERICIA (sec) 0,415 + 0,019 vs 0,433 + 0,046 (with P = 0,094), QTc FRAMINGHAM (sec) 0,415 + 0,018 vs 0,428 + 0,030 (with P = 0,079), QTc HODGES (sec) 0,415 + 0,018 vs 0,428 + 0,034 (with P = 0,141) and Tpeak to Tend index 94,800 ± 14,877 vs 94,150 ± 12,877

(with P < 0,824), confirming the safety of Gliatilin^{R} in elderly patients (Tab. 1). The treatment was well tolerated in routine clinical practice. All patients started study drug and no subjects were excluded after the patient run-in period due to the absence of transient adverse events.

DISCUSSION

- **Main results**

A statistically significant improvement of the MMSE value (18,692 ± 3,881 vs 21,077 ± 4,010) (with P < 0,001*****) after 30 days (Fig. 3) and MMSE value (19,714 ± 5,693 vs 19,905 ± 6,449 (with P = 0,047*****) after 90 days of the treatment with (Gliatilin^{R}) (2) has been observed (Fig. 4). No significant differences in HRV explored in the time domain: SDNN 17,375 ± 10,715 vs 22,235 ± 27,631 (with P = 0,327); RMSSD 13,910 ± 6,373 vs 23,385 ± 41,318 (with P = 0,295); explored in the frequencies domain LF 61,580 ± 23,138 vs 61,360 ± 22,201 (with P = 0,972); HF 38,320 ± 23,095 vs 38,500 ± 22,138 (with P = 0,974); LF/HF 2,929 ± 3,047 vs 2,804 ± 2,583 (with P = 0,889); explored with non-linear analyses DFA alpha-1 1,077 ± 0,344 vs 1,069 ± 0,287 (with P = 0,919); DFA alpha-2 0,497 ± 0,187 vs 0,497 ± 0,196 (with P = 0,982); SD1 9,850 ± 4,519 vs 16,570 ± 29,275 (with P = 0,295); SD2 22,150 ± 14,859 vs 25,930 ± 26,719 (with P = 0,372); Approximate Entropy 1,006 ± 0,163 vs 1,030 ± 0,138 (with P = 0,417); Sample Entropy 1,546 ± 0,381 vs 1,649 ± 0,485 (with P = 0,339); Shannon Entropy 3,091 ± 0,358 vs 2,954 ± 0,582 (with P = 0,253); (10) arrhythmic index QT interval (msec) 387,700 ± 33,545 vs 398,350 ± 31,423 (with P < 0,132) (Fig. 7) QTc BAZZET (sec) 0,430 + 0,021 vs 0,447 + 0,048 (with P = 0,11), QTc FREDERICIA (sec) 0,415 + 0,019 vs 0,433 + 0,046 (with P = 0,094), QTc FRAMINGHAM (sec) 0,415 + 0,018 vs 0,428 + 0,030 (with P = 0,079), QTc HODGES (sec) 0,415 + 0,018 vs 0,428 + 0,034 (with P = 0,141) and Tpeak to Tend index 94,800 ± 14,877 vs 94,150 ± 12,877 (with P < 0,824) (Fig. 8) have been observed, confirming the safety of (Gliatilin^{R}) in elderly patients (5).

The absence of any statistically significant modification of the QT (Fig. 7), QTc and Tp/Te index (Fig. 8) is a significant clinical advantage, because it permits to exclude a correlation with arrhythmic risk.

- **comparison with finding reported in the literature**

The literature data confirm the positive effect on cognitive tests, during treatment in elderly patients suffering from cognitive impairment (2). There are few works regarding specifically the assessment of arrhythmic risk (10) on a large scale, as it is often adopted only for patients treated with drugs for behavioural stabilization in the more advanced stages of Alzheimer's disease.

- **study design choices**

The choice of study design is linked to the need to use standardized tests and variables to carry out a repeatable and comparable scientific evaluation. For this reason, the Mini Mental State Examination was chosen as a cognitive test, and the analysis of HRV explored in time domain (SDNN, RMSSD), in the frequencies domain (LF, HF, LF/HF), with non linear analyses (DFA alpha-1, DFA alpha-2, SD1, SD2, approximate entropy, sample entropy, Shannon entropy) (10), QT and Tpeak to T end for the arrhythmias risk assessment.

- Strengths and limitations of the study

– **Strengths**

The study was carried out including a modest number of patients enrolled, but the strength of the study derives from the great significance of the values of the variables measured before and after treatment.

– **Limitations**

The limitation of the study is linked to the average age of the patients enrolled which does not allow the data to be generalized to the entire elderly population.

– **Perspectives**

The future prospect is to analyse data relating to a longer follow-up period, to verify the effect of the treatment at 9 months and 12 months, compared to baseline conditions.

CONCLUSION

The study was designed to provide evidence to support the efficacy (2) of choline alphoscerate (Gliatilin^{R}) treatment in managing of Dementia in elderly patients (5). The data of the study underline that the treatment statistically improves the Mini Mental State Examination test (Fig. 5-6). No significant modifications are noted about cardiovascular risk evaluation (Table 1). There is no statistically significant change in arrhythmic risk evaluated exploring HRV explored in time domain (SDNN, RMSSD), in the frequencies domain (LF, HF, LF/HF), with non linear analyses (DFA alpha-1, DFA alpha-2, SD1, SD2, approximate entropy, sample entropy, Shannon entropy), (10) QT (Fig. 7), QTc and Tpeak to T end indices (Fig. 8). This experience has permitted to use choline alphoscerate in elderly patients with Dementia.

Author Contributions

Prof./Dr. Marchitto Nicola for study conception and design, analysis and interpratation; Dott.ssa Paparello Paola Tamara for patients enrollment, follow-up evaluation by MMSE and EKG registration; Dott.ssa Manfrini Giulia for coordinative aspects; Dott. Piazza Roberto , Dott.ssa Coco Ilaria, Dott.ssa Pacella Chiara for revision of the manuscript and Prof. Raimondi Gianfranco for final approval.

conflict of interest statement

All authors have not competed interests in connection with this study.

ethical statement

The authors certify that they comply with the ethical guidelines.

Human Ethics and Consent to Participate declarations: The study was performed in compliance with the declarations of human ethics and consent to participate.

Sponsor's role and Funding Declaration: there was no Funding for the study.

Clinical Trial Number: not applicable for retrospective observational study.

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Conflict of Interest: none declared

ORCID

Prof./Dr. Marchitto Nicola ORCID number: 0000-0003-1271-8848.

TABLES

	CONTROL ± SD	EFFECT ± SD	Probability (P)
MMSE (0-30) (T0-T1)	18,692 ± 3,881	21,077 ± 4,010	0,001*
MMSE (0-30) (T0-T3)	19,714 ± 5,693	19,905 ± 6,449	0,047*
RR variability	825,555 ± 142,645	809,450 ± 138,192	0,448
SDNN	17,375 ± 10,715	22,235 ± 27,631	0,327
RMSSD	13,910 ± 6,373	23,385 ± 41,318	0,295
LF	61,580 ± 23,138	61,360 ± 22,201	0,972
HF	38,320 ± 23,095	38,500 ± 22,138	0,974
LF/HF	2,929 ± 3,047	2,804 ± 2,583	0,889
DFA (alpha-1)	1,077 ± 0,344	1,069 ± 0,287	0,919
DFA (alpha-2)	0,497 ± 0,187	0,497 ± 0,196	0,982
SD1	9,850 ± 4,519	16,570 ± 29,275	0,295
SD2	22,150 ± 14,859	25,930 ± 26,719	0,372
Approximate Entropy	1,006 ± 0,163	1,030 ± 0,138	0,417
Sample Entropy	1,546 ± 0,381	1,649 ± 0,485	0,339
Shannon Entropy	3,091 ± 0,358	2,954 ± 0,582	0,253
QT (msec)	387,700 + 33,545	398,350 + 31,423	0,132
QTc BAZZET (sec)	0,430 + 0,021	0,447 + 0,048	0,105
QTc FREDERICIA (sec)	0,415 + 0,019	0,433 + 0,046	0,094
QTc FRAMINGHAM (sec)	0,415 + 0,018	0,428 + 0,030	0,079
QTc HODGES (sec)	0,415 + 0,018	0,428 + 0,034	0,141
Tpeak to Tend (msec)	94,800 + 14,877	94,150 + 12,877	0,824
Tpeak to Tend/QT	0,24	0,23	Ns

Table 1: Descriptive Statistics about Mini Mental State Examination (MMSE) evaluated before and after treatment with choline alphoscerate (Gliatilin^{R}) at a dosage of 600 mg orally administered 2 times a day for 30 Days (T1) and 90 days (T2). Arrhythmic index are evaluated before (T0) and after 30 days (T1). Paired T test data are expressed as mean ± Standard Deviation (SD).

	Base (T0) Run-in periods	Control (T1) 30 days	Control (T2) 90 days	Probability (P ≤ 0,050)
ANOVA (MMSE)	19,714 ± 5,693	20,667 ± 5,219	19,905 ± 6,449	0,049 *
ANOVA (MMSE-c)	19,995 ± 5,467	21,095 ± 4,962	20,329 ± 6,147	0,049 *

Table 2: Descriptive Statistics about Mini Mental State Examination standard (MMSE-s) and Mini Mental State Examination corrected for age and scholarity (MMSE-c) evaluated before and after treatment with choline alphoscerate (Gliatilin^{R}) at a dosage of 600 mg administered orally 2 times a day for 30 Days (T1) and 90 days (T2). Anova data are expressed as mean ± Standard Deviation (SD).

FIGURES

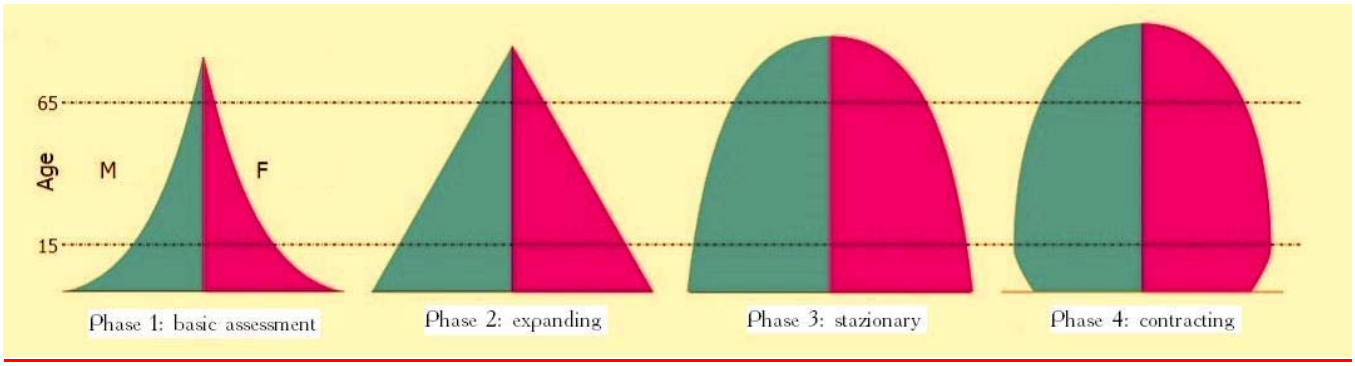

Fig. 1. Graphic representation of the modifications of the Italian population represented by Lexis pyramids.

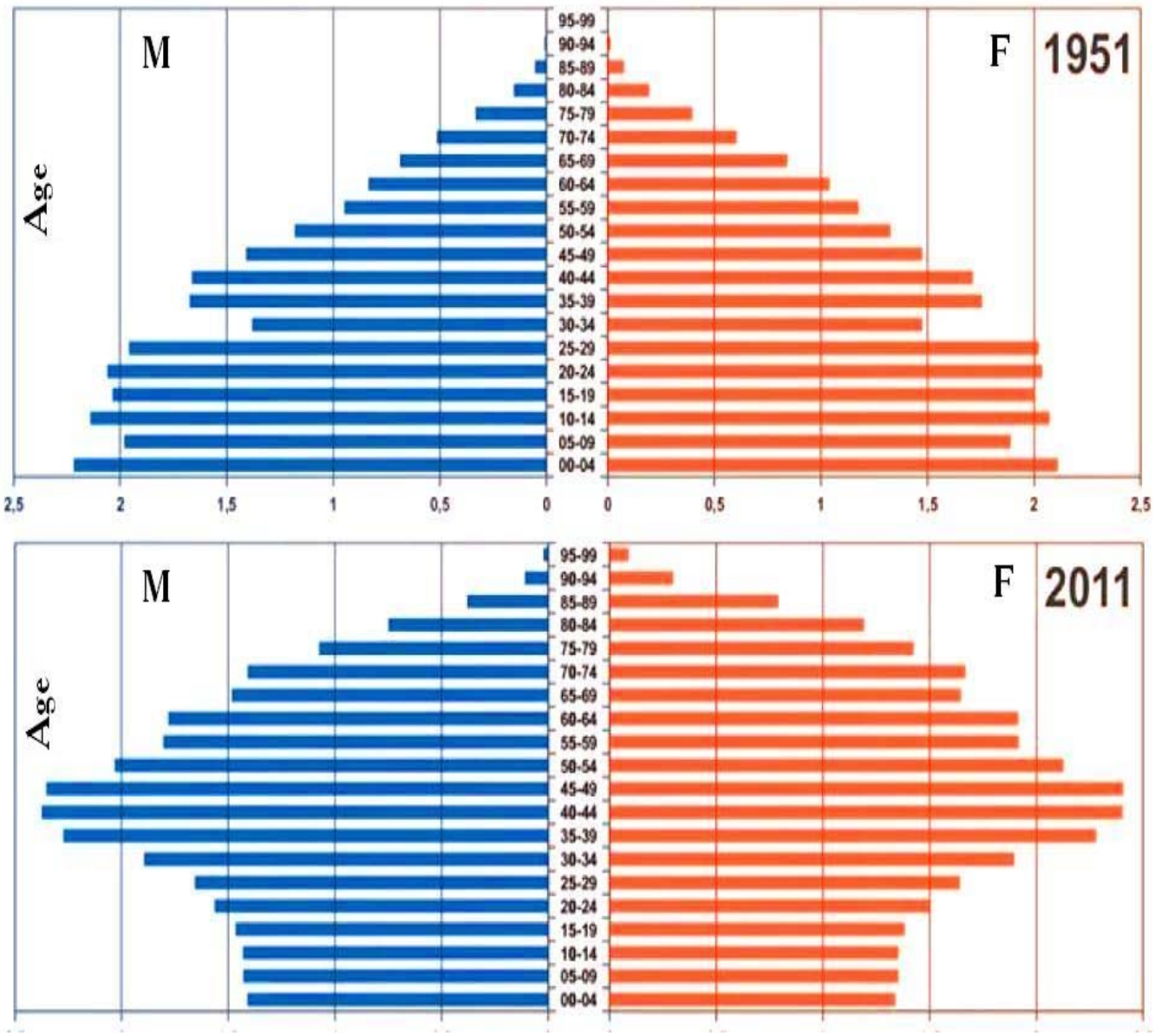

Fig. 2. Graphic representation of the modifications of the Italian population represented by Lexis pyramids. The progressive increase in the elderly population and the progressive reduction in the birth rate (contracting phase of population growth) appear evident.

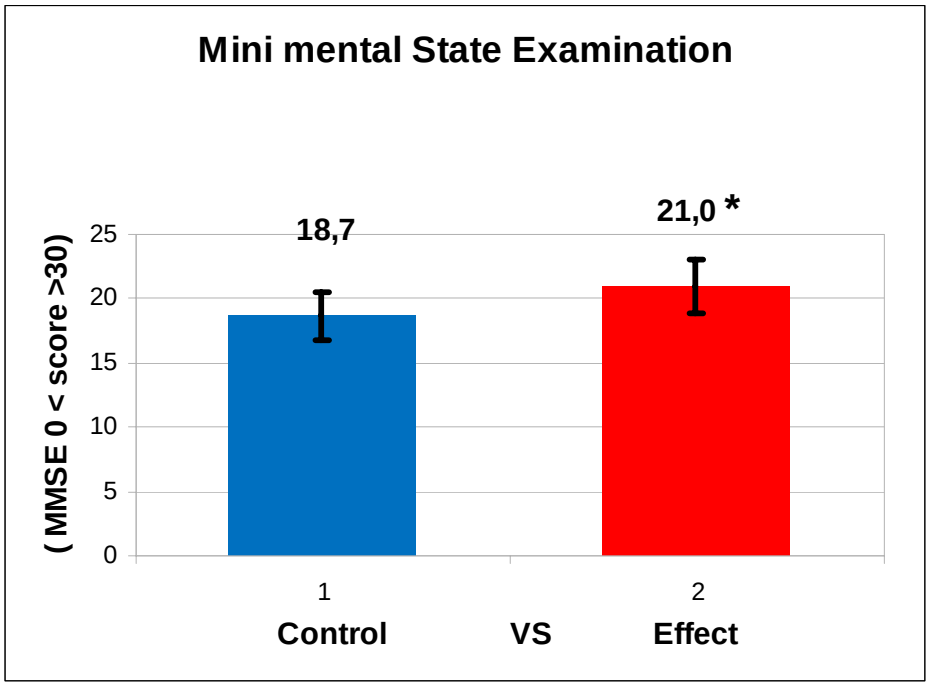

Fig. 3: Descriptive statistic about Mini Mental State Examination test (MMSE) modification before (T0) and after 30 days treatment period (T1) with choline alphoscerate (Gliatilin[R]). Data are expressed as mean ± Standard Deviation (SD).

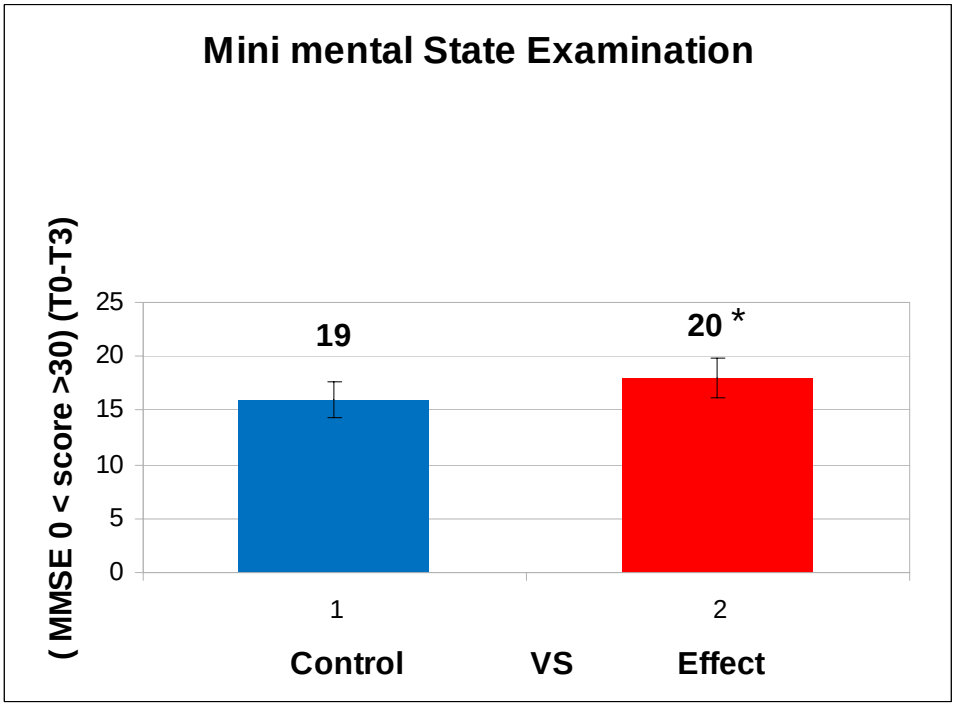

Fig. 4: Descriptive statistic about Mini Mental State Examination test (MMSE) modification before (T0) and after 90 days treatment period (T2) with choline alphoscerate (Gliatilin[R]). Data are expressed as mean ± Standard Deviation (SD).

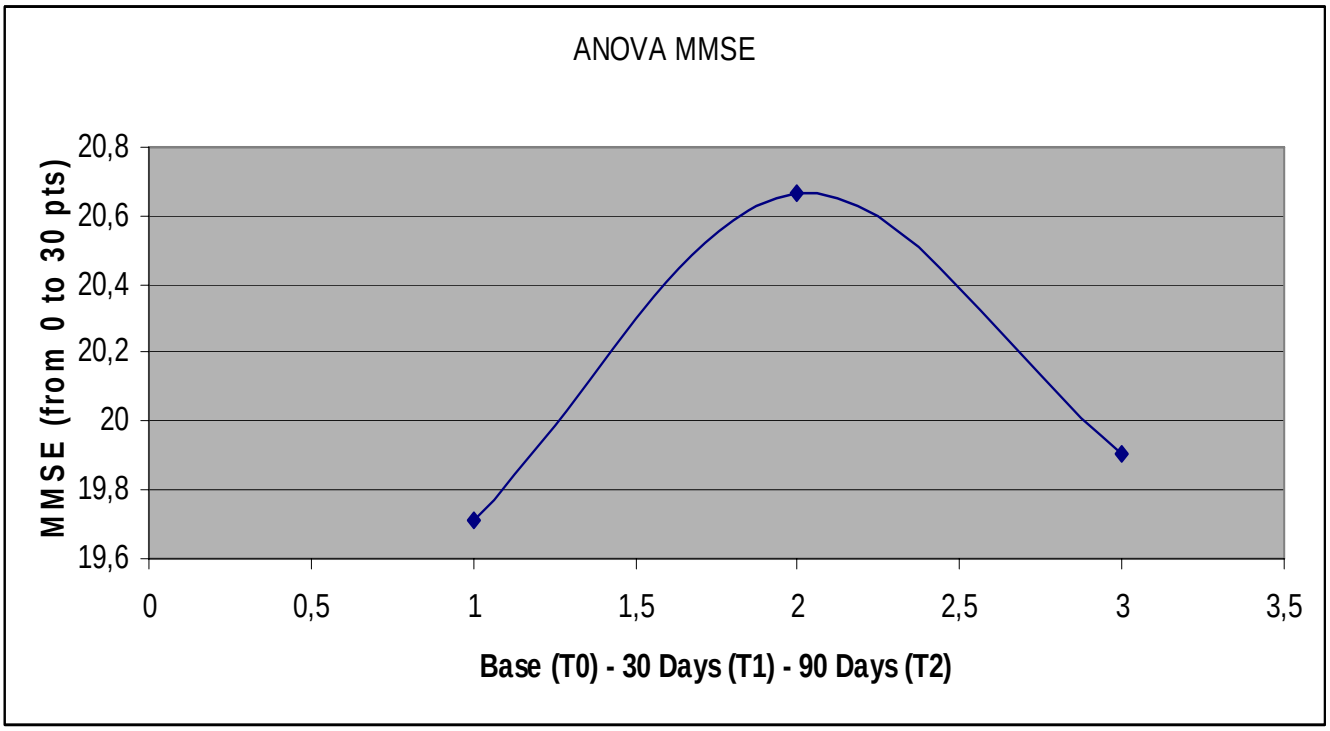

Fig. 5: Descriptive statistic about Mini Mental State Examination test (MMSE) modification in basal condition (T0), after 30 days (T1) and 90 days (T2) after treatment with choline alphoscerate (Gliatilin^{R}). Data are expressed as mean ± Standard Deviation (SD).

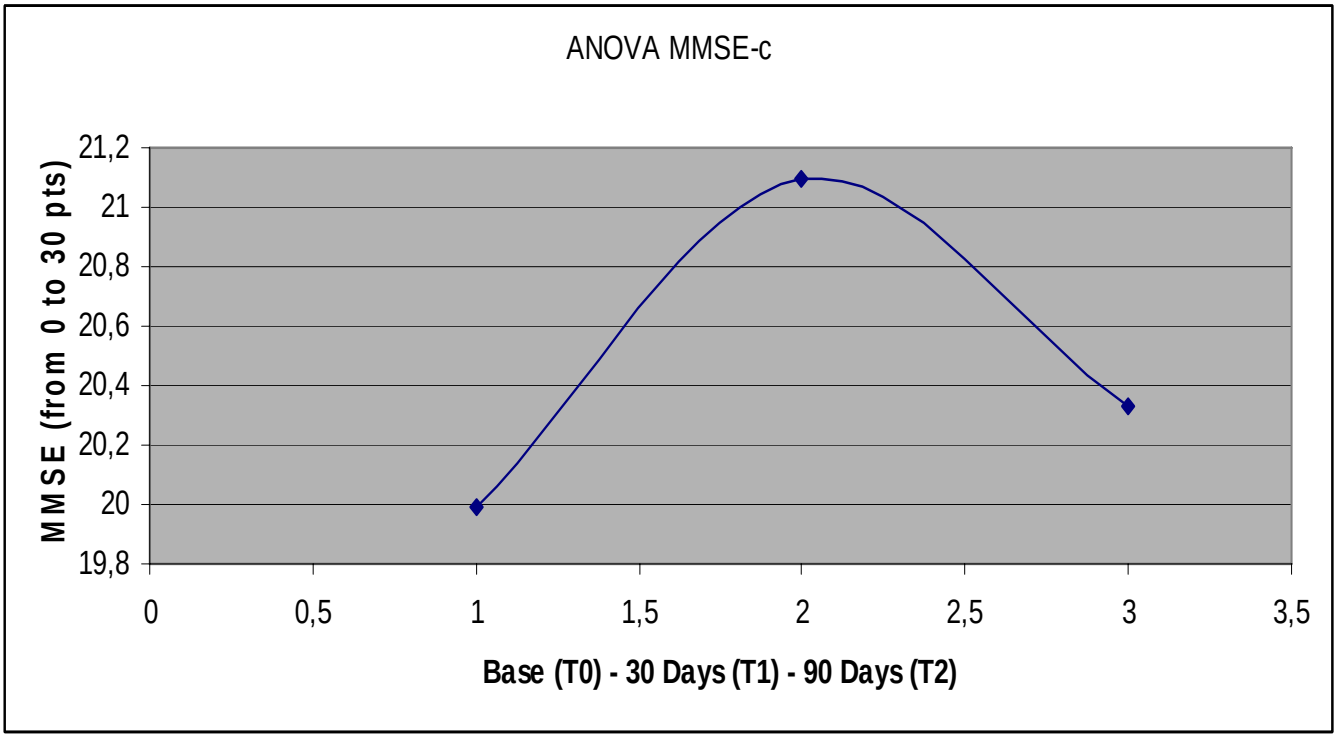

Fig. 6: Descriptive statistic about Mini Mental State Examination test (corrected for age and scholarity or MMSE-c) modification in basal condition (T0), after 30 days (T1) and 90 days (T2) after treatment with choline alphoscerate (Gliatilin^{R}). Data are expressed as mean ± Standard Deviation (SD).

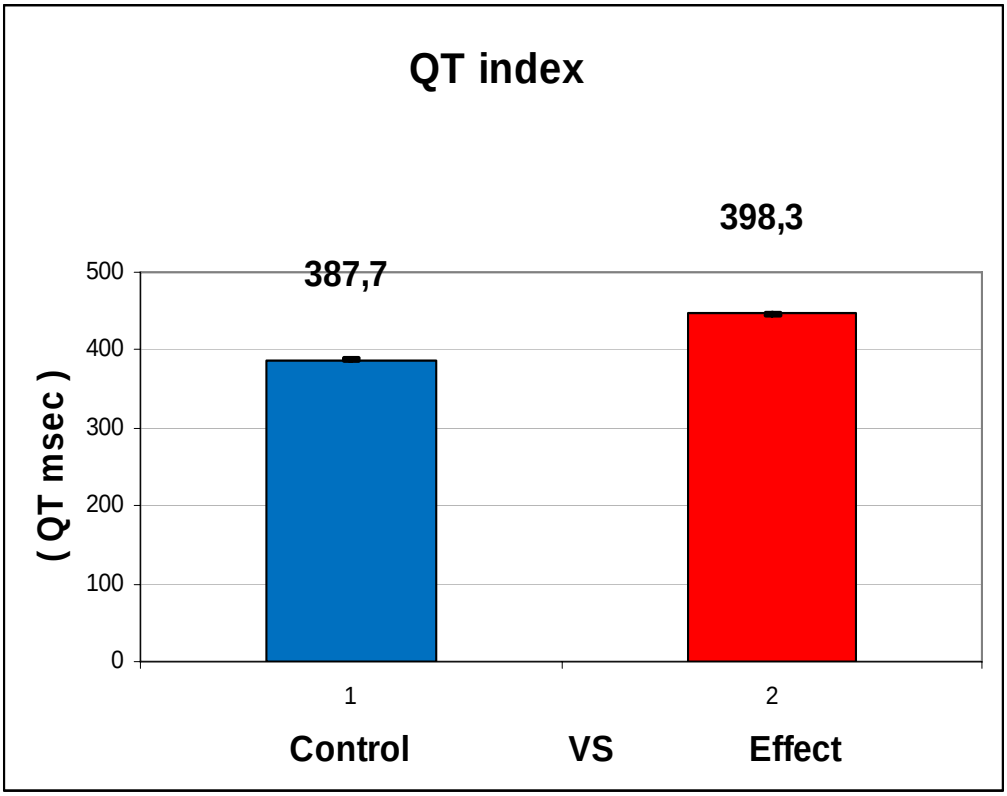

Fig. 7: Descriptive statistic about QT index modification before (T0) and after 30 Days (T1) of treatment period with choline alphoscerate (Gliatilin[R]). Data are expressed as mean ± Standard Deviation.

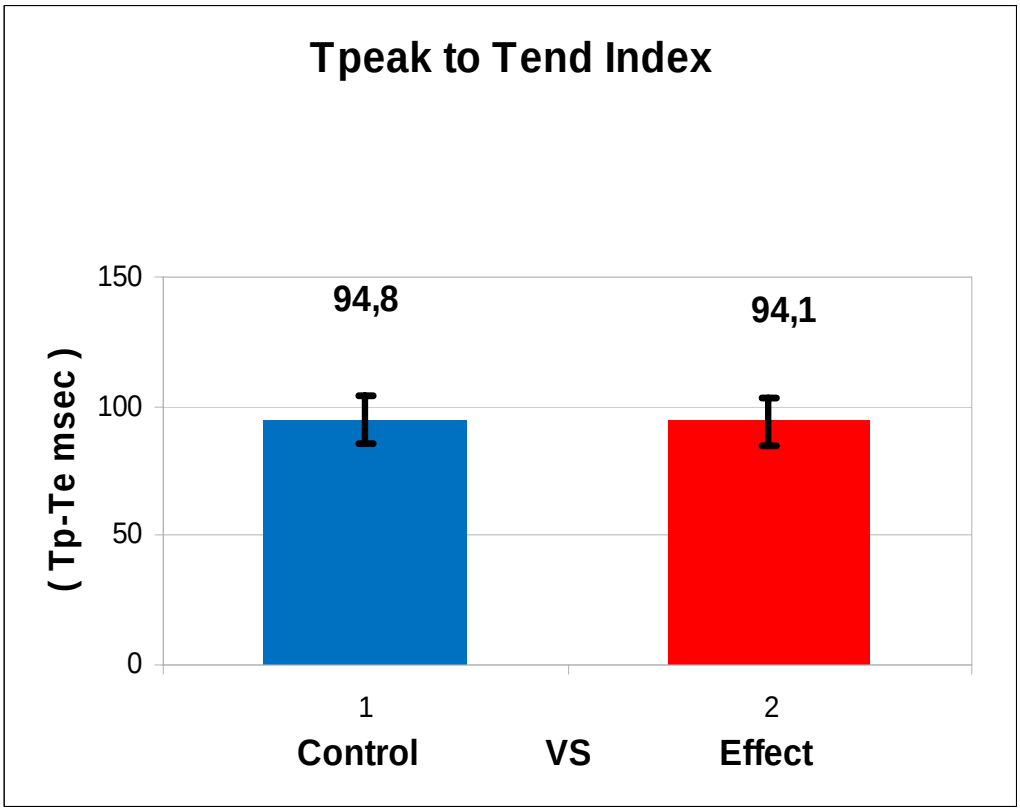

Fig. 8: Descriptive statistic about Tpeak to Tend index modification before (T0) and after 30 Days (T1) of treatment period with choline alphoscerate (Gliatilin[R]). Data are expressed as mean ± Standard Deviation.

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