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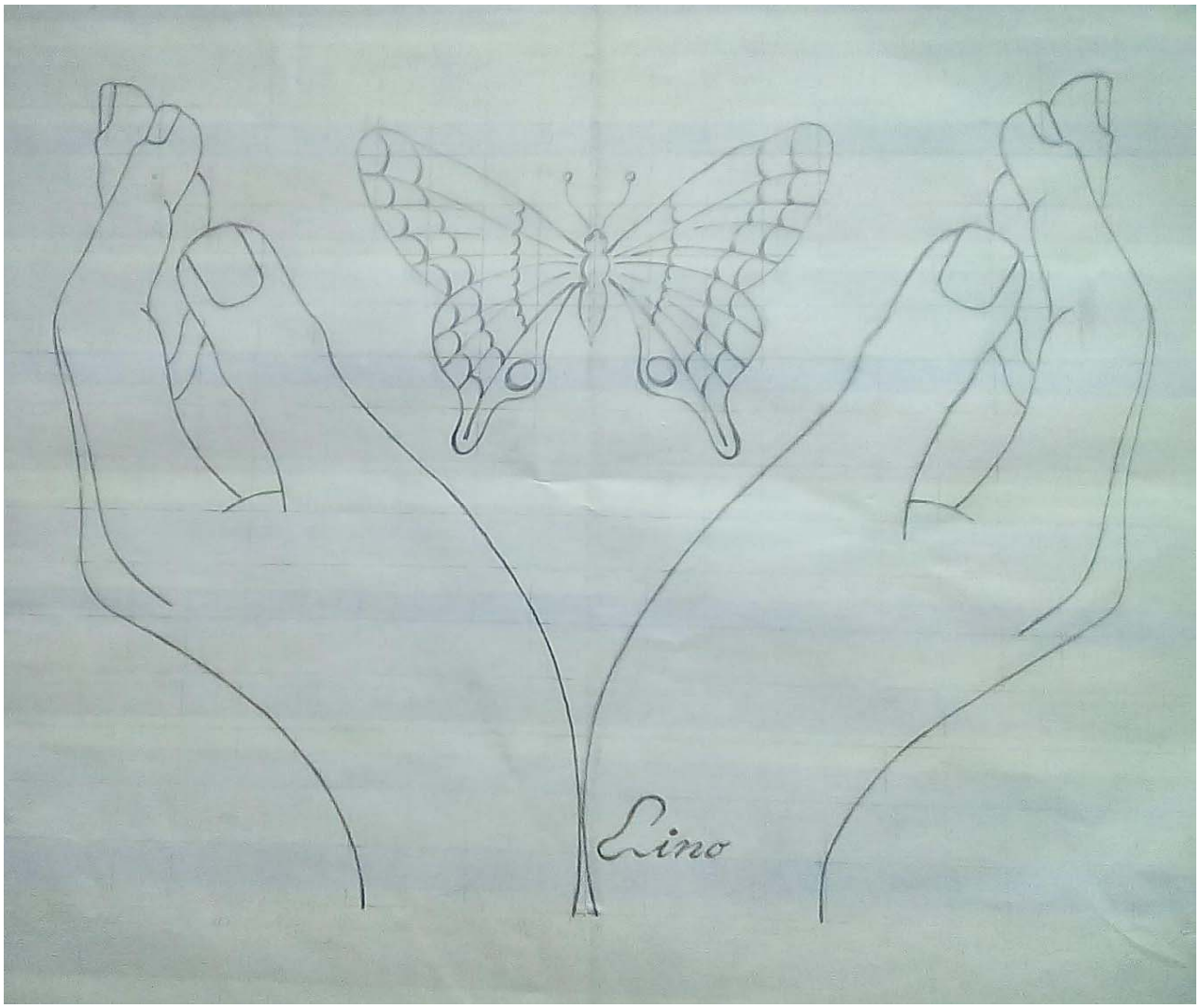

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DECADIMENTO COGNITIVO: EFFICACIA E SICUREZZA CARDIOVASCOLARE DI UN NUTRACEUTICO A BASE DI OMOTAURINA, DHA MICROINCAPSULATO, NADH, MAGNESIO SUCROSOMIALE, OXYCIAN, VITAMINA B12 (PROCOGNITIV^{R}).

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KEYWORDS: decadimento cognitivo, MMSE, Qtc, Tp-Te, rischio cardiovascolare.

ABSTRACT

Introduzione: Negli ultimi anni i nutraceutici hanno notevolmente ampliato le opzioni terapeutiche disponibili per il trattamento di numerose patologie acute e croniche. Tale aspetto si è reso evidente anche nell'ambito del trattamento del decadimento cognitivo. L'approccio nutraceutico offre attualmente nuove opzioni di trattamento di associazione che consentono di migliorare il profilo cognitivo e rallentare l'evoluzione della malattia. La letteratura internazionale riporta anche segnalazioni di aumento del rischio di aritmie correlato all'uso di farmaci per il trattamento del decadimento cognitivo. I principali indici di rischio aritmico riconosciuti a livello internazionale sono l'indice QT, l'indice Qtc e l'indice Tpeak-to-Tend. Solo alcuni di questi indici sono utilizzati nella pratica clinica (QT) mentre gli altri sono utilizzati nella ricerca scientifica, per la stratificazione del rischio aritmico, data la complessità della valutazione. **Obiettivo:** Lo scopo di questo studio è valutare l'efficacia e la sicurezza dell'associazione di Omotaurina, DHA microincapsulato, NADH, Magnesio sucrosomiale, Oxycian, Vitamina B12 (Procognitiv^{R}) in associazione al trattamento standard nei pazienti geriatrici affetti da deterioramento cognitivo. **Materiali e Metodi:** Il presente studio è stato progettato per indagare l'efficacia e la sicurezza del Procognitiv^{R} in aggiunta al trattamento standard per il decadimento cognitivo. L'efficacia è stata valutata utilizzando il test Mini Mental State Examination (MMSE) mentre la sicurezza è stata valutata, mediante l'analisi dei principali indici aritmici riportati nella letteratura internazionale (QT, QTc, Tpeak-Tend). In questo

progetto di studio pilota, sono stati arruolati 343 pazienti. Al termine del periodo di osservazione i pazienti che avevano completato il follow-up erano 341 (63 maschi e 278 femmine, età media 77,5 ± 10 anni) affetti da declino cognitivo (MMSE medio 18/30 ± 4) già in trattamento standard. Durante il periodo di arruolamento, i pazienti sono stati sottoposti a valutazione cognitiva utilizzando il test MMSE ed a registrazione elettrocardiografica non invasiva, al fine di valutare l'effetto del trattamento aggiuntivo con Procognitiv^{R} in relazione al rischio aritmico cardiovascolare esplorato con l'analisi di QT, Qtc e Tpeak to Tend Index (Tp/Te). Il trattamento proposto era Procognitiv^{R} alla posologia di due capsule giornaliere (150 mg di Omotaurina/die) per 1 mese, aggiunto al trattamento già in atto per il trattamento del deterioramento cognitivo. I dati sono stati misurati con il software cardiolab xai-medica e analizzati utilizzando il software SigmaStat 3.5 per Windows. **Risultati:** È stato osservato un miglioramento statisticamente significativo del valore MMSE (16,857 $\pm$ 4,096 vs 17,964 $\pm$ 4,138 con P < 0,001 *) dopo 1 mese di trattamento con Procognitiv^{R} aggiunti al trattamento standard per il decadimento cognitivo. È stata inoltre osservata una variazione ai limiti della significatività statistica dell'indice QT (Tab. 1). Essendo il valore del QT influenzato dalla frequenza cardiaca, la valutazione del rischio aritmico è stata integrata mediante il calcolo del QT corretto per la frequenza cardiaca del soggetto preso in esame (Qtc) utilizzando la formula di Bazzet, di Fredericia, di Framingham, di Hodges e di Rautaharju. Tale analisi ha consentito di evidenziare riduzioni statisticamente significative dei valori di Qtc dopo 1 mese di trattamento con normalizzazione dei valori nei pazienti con parametri di rischio aritmico (Qtc > 450 msec ♂ e > 480 msec ♀). **Discussione:** I dati della Tabella 1 mostrano che il trattamento con Procognitiv^{R}, aggiunto al trattamento standard, determina un incremento statisticamente significativo dei punteggi medi del MMSE (16,857 $\pm$ 4,096 vs 17,964 $\pm$ 4,138 con P < 0,001 *) nei pazienti con declino cognitivo già dopo il primo mese di trattamento. Nella letteratura internazionale sono riportati studi che evidenziano la presenza di alterazioni della modulazione neurovegetativa con ipertonicità simpatica prevalentemente durante la notte e nelle prime ore del mattino durante il trattamento con farmaci anticolinesterasici in pazienti con declino cognitivo senile. La valutazione dei dati relativi allo studio ci consente di affermare che la terapia di associazione con Procognitiv^{R}, aggiunta alla terapia standard per il decadimento

cognitivo, determina una riduzione statisticamente significativa del valore QTc, già dopo il primo mese, valutato con le formule di Bazzet (458,375 ± 28,687 vs 412,938 ± 15,648 con P < 0,001*) (Fig. 2), Fredericia (452,857 ± 29,784 vs 407,625 ± 22,238 con P < 0,001*) (Fig. 3), Framingham (450,438 ± 30,301 vs 408,500 ± 20,954 con P < 0,001*) (Fig. 4), Hodges (453,063 ± 29,794 vs 409,000 ± 27,281 con P < 0,001*) (Fig. 5) e Rautaharju (454,500 ± 28,733 vs 409,313 ± 22,650 P < 0,001*) (Fig. 6), evidenziando la sicurezza del trattamento di associazione Procognitiv^{R} nei soggetti anziani. **Conclusioni:** Lo studio pilota da noi condotto ci ha permesso di evidenziare, attraverso la valutazione del MMSE e del rischio aritmico, l'effetto sinergico dell'associazione nutraceutica Procognitiv^{R} nel trattamento del decadimento cognitivo senile. Il nostro studio ci ha permesso di scoprire la normalizzazione degli indici di rischio aritmico cardiovascolare durante il trattamento con Procognitiv^{R}, aggiunto al trattamento standard, in contrasto a quanto riportato in articoli scientifici della letteratura internazionale in merito all'ipertonicità simpatica e quindi al rischio aritmico indotto dal trattamento standard o con farmaci anticolinesterasici. Pertanto, sulla base di dati preliminari, il ruolo di Procognitiv^{R} appare essenziale nel miglioramento del profilo cognitivo e nella contemporanea riduzione del rischio aritmico. Poiché Procognitiv^{R} è un nutraceutico contenente più molecole attive, è difficile identificare il ruolo antiaritmico dei singoli componenti attivi presenti nel nutraceutico o il loro possibile effetto sinergico. Attualmente, il campione in esame è stato valutato dopo il primo mese di terapia e continua ad essere monitorato in follow-up a cadenza trimestrale. I dati già raccolti e l'analisi dei dati di follow-up successivi consentiranno di estrapolare dati definitivi sull'andamento trimestrale, semestrale o annuale del trattamento e consentiranno di esprimere una valutazione estendibile a tutta la popolazione over 65.

Punti chiave dello studio

1) **Efficacia:** Nella letteratura scientifica internazionale non sono presenti studi, basati su test standardizzati, che evidenzino l'efficacia del trattamento con l'associazione di Omotaurina, DHA microincapsulato, NADH, Magnesio sucrosomiale, Oxycian, Vitamina B12

(Procognitiv^{R}) in pazienti affetti da declino cognitivo.

2) **Sicurezza:** La letteratura internazionale riporta che la somministrazione di alcune classi di farmaci determina un aumento dell'incidenza di aritmie maggiori (1). Questo aspetto è particolarmente importante nei pazienti anziani sottoposti a trattamento polifarmacologico per deterioramento cognitivo e altre comorbilità in quanto espone il paziente a un rischio elevato di interazioni farmacologiche. L'effetto finale dei trattamenti polifarmacologici nei pazienti anziani è dose-dipendente. Può anche essere legato alla necessità di aumentare il dosaggio per peggioramento dei sintomi o tolleranza al trattamento, con concomitante aumento del rischio di aritmie pericolose per la vita (1).

Perchè questo studio è importante? Il trattamento polifarmacologico del decadimento cognitivo rappresenta una condizione clinica sempre più emergente in relazione all'aspettativa di vita media della popolazione. Il rischio di aritmie è più elevato nella popolazione anziana sottoposta a trattamento polifarmacologico (1). Pertanto è fondamentale proporre trattamenti farmacologici efficaci e sicuri sottoposti a una valutazione del rischio di aritmia basata su evidenze scientifiche (1) al fine di minimizzare, o eventualmente eliminare, il rischio aritmico del paziente.

Introduzione

Negli ultimi anni i nutraceutici hanno notevolmente ampliato le opzioni terapeutiche disponibili per il trattamento di numerose patologie acute e croniche. Tale aspetto si è reso evidente anche nell'ambito del trattamento del decadimento cognitivo. L'approccio nutraceutico offre attualmente nuove opzioni di trattamento di associazione che consentono di migliorare il profilo cognitivo e rallentare l'evoluzione della malattia. La letteratura internazionale riporta anche segnalazioni di aumento del rischio di aritmie correlato all'uso di farmaci per il trattamento del decadimento cognitivo. I principali indici di rischio aritmico riconosciuti a livello internazionale sono l'indice QT, l'indice Qtc e l'indice Tpeak-to-Tend. Solo alcuni di questi indici sono utilizzati nella pratica clinica

(QT) mentre gli altri sono utilizzati nella ricerca scientifica, per la stratificazione del rischio aritmico, data la complessità della valutazione.

Obiettivo dello studio: Lo scopo di questo studio è valutare l'efficacia e la sicurezza dell'associazione di Omotaurina, DHA microincapsulato, NADH, Magnesio sucrosomiale, Oxycian, Vitamina B12 (Procognitiv^{R}) in associazione al trattamento standard nei pazienti geriatrici affetti da deterioramento cognitivo (Tab. 1).

MATERIALI e METODI

Participanti ed approvazione etica

Nel febbraio 2023 è stato avviato presso il Dipartimento di Medicina Generale e l'ambulatorio di Geriatria dell'Ospedale San Giovanni di Dio di Fondi, Latina (Italia) uno studio osservazionale sull'efficacia e la sicurezza del trattamento del decadimento cognitivo basato sull'associazione di Procognitiv^{R} alle terapie farmacologiche standard. E' stato richiesto il consenso informato per il trattamento dei dati sensibili e per le misurazioni elettrocardiografiche non invasive, eseguite in condizioni basali e dopo trattamento farmacologico con l'associazione di Procognitiv^{R} aggiunto alla terapia standard. L'arruolamento nello studio è stato volontario. Ai pazienti e ai caregiver è stato rilasciato un consenso informato che spiega in dettaglio il razionale dello studio, le modalità operative e la possibilità di interrompere il follow-up in qualsiasi momento. I dati sensibili sono stati trattati nel rispetto della normativa sulla Privacy. Lo studio pilota è iniziato a Febbraio 2023 e si è basato sulla raccolta e l'elaborazione dei dati dei pazienti dell'ambulatorio di Geriatria dell'Ospedale San Giovanni di Dio di Fondi (Latina). I dati dello studio sono relativi a 341 (63 maschi e 278 femmine, età media 77,5 ± 10 anni) affetti da declino cognitivo (MMSE medio 18/30 ± 4) già in trattamento standard per compromissione cognitiva.

- **Raccolta dei dati**

Tutti i pazienti arruolati nello studio hanno fornito il loro consenso informato allo studio osservazionale. Tutti i pazienti hanno continuato i trattamenti farmacologici standard nel rispetto

delle linee guida etiche. Per quanto riguarda l'uso della scala, è stata standardizzata al sistema di riferimento internazionale per i test di laboratorio e i test strumentali. I requisiti di ammissibilità allo screening includevano l'età di almeno 18 anni. Tutti i pazienti hanno fornito il consenso informato scritto per la raccolta dei dati. Tutti i pazienti arruolati nello studio hanno fornito il loro consenso informato allo studio osservazionale.

- **Criteri di inclusione e di esclusione**

I criteri di inclusione considerano la presenza di compromissione cognitiva valutata con Mini Mental State Examination (MMSE) e un'età superiore ai 65 anni. Il criterio di inclusione richiesto per l'arruolamento è rappresentato da un valore MMSE 18/30 $\pm$ 4, nei pazienti con compromissione cognitiva lieve.

I criteri di esclusione sono riconducibili alla tecnica di analisi elettrocardiografiche del rischio aritmico che non consentono di valutare pazienti con anomalie del ritmo o fibrillazione atriale. Pertanto, i criteri di esclusione includevano il trattamento con farmaci antiaritmici e la presenza di Dispositivo Cardiaco Impiantabile (ICD) per la possibile interferenza nella valutazione del rischio aritmico rispetto alla popolazione in ritmo sinusale. I pazienti con difficoltà dovute a limitazioni funzionali, con impossibilità di recarsi in ospedale per il follow-up, non sono inclusi nello studio.

- **Variabili principali esaminate**

Lo studio è stato progettato per valutare la funzione cognitiva utilizzando il test standardizzato Mini Mental State Examination (MMSE) (Tab. 1). Per valutare il rischio aritmico è stata eseguita una registrazione elettrocardiografica digitale della durata di 3 minuti o di almeno 250 battiti cardiaci. Dall'analisi dell'intervallo QT, Qtc e dell'indice Tpeak to T end è stato possibile valutare il rischio aritmico prima e dopo il trattamento farmacologico associato a Procognitiv^{R} (Tab. 1). Per quanto riguarda l'uso della scala, essa è stata standardizzata al sistema di riferimento internazionale per esami di laboratorio e per esami strumentali.

- **Covariabili**

Il trattamento con farmaci antiaritmici può alterare la valutazione elettrocardiografica degli

indici aritmici nei pazienti affetti da cardiopatia cronica, pertanto le registrazioni elettrocardiografiche sono state eseguite mantenendo il trattamento domiciliare standard, senza ulteriori aumenti di dosaggio, per evitare distorsioni della variabilità della frequenza cardiaca e dei valori degli indici aritmici Tpeak-to-Tend (2-3), QT (4), Qtc (5-6).

- **Risultati attesi**

I risultati attesi dallo studio sono la conferma dell'efficacia sull'aspetto cognitivo MMSE del trattamento con Procognitiv^{R} in aggiunta alla terapia standard e della sicurezza data dallo studio dell'indice QTc.

- **Disegno dello studio**

Il disegno dello studio era finalizzato ad analizzare la funzione cognitiva utilizzando il test standardizzato Mini Mental State Examination (MMSE). Per valutare il rischio aritmico, è stata eseguita una registrazione elettrocardiografica digitale non invasiva per circa 3 minuti (o 250 battiti cardiaci). Utilizzando algoritmi matematici computerizzati per il calcolo dell'intervallo Tpeak-to-Tend (2-3), QT (4), Qtc (5-6), è stato possibile valutare il rischio aritmico prima e dopo il trattamento con Procognitiv^{R} in aggiunta alla terapia standard per il declino cognitivo. Al momento dell'arruolamento, è stato avviato un periodo di run-in per sottoporre tutti i pazienti arruolati a registrazione elettrocardiografica digitale non invasiva a 12 derivazioni, al fine di valutare l'effetto di Procognitiv^{R}, in aggiunta alla terapia standard per il declino cognitivo, sul rischio aritmico cardiovascolare mediante valutazione del QT, del Qtc e dell'indice Tpeak to Tend (Tp/Te). I tre diversi indici di rischio cardiovascolare sono stati valutati mediante tracciato elettrocardiografico in condizioni basali (T0) e dopo 30 giorni (T1) di trattamento con Procognitiv^{R} (Tab. 1). Il trattamento viene eseguito utilizzando la posologia di 2 capsule/die (150 mg di Omotaurina/die), per 30 giorni.

- **Analisi Statistica**

I dati sono stati misurati utilizzando il software cardiolab Xai-medica e analizzati con il software SigmaStat 3.5 per Windows XP. Il test ANOVA per l'analisi di dati è stato utilizzato per elaborare i dati pre e post trattamento registrati negli stessi

soggetti arruolati nello studio. Il test ANOVA per dati appaiati consente di eseguire analisi statistiche comparative in gruppi di pazienti superiori alle 30 unità (Tab. 1). La significatività statistica è stata fissata a $P < 0,05$.

RESULTATI

- **Diagramma di flusso dello studio**

Valutazione di base utilizzando il test

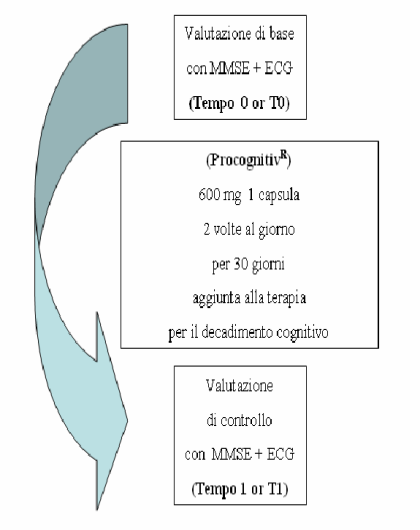
MMSE + ECG (T0) =>

trattamento con Procognitiv^{R}

in aggiunta alla terapia standard per il decadimento cognitivo =>

Rivalutazione di controllo dopo 30 giorni utilizzando il test

MMSE + ECG (T1).



Rappresentazione grafica del diagramma di flusso dello studio.

- **Caratteristiche di base dello studio**

L'età media dei 341 pazienti arruolati era di 77,5 ± 10 anni. Il gruppo di pazienti che ha completato il periodo di follow-up era composto da 63 uomini e 278 donne. Tutti i pazienti arruolati hanno un profilo di rischio cardiovascolare elevato e una pressione sanguigna normale (con trattamento farmacologico). Da febbraio 2023 un totale di 341 pazienti sono entrati nel periodo di run-in. Tutti i dati dei pazienti rispettano i criteri dello studio. Nessun paziente è stato randomizzato per errore o è stato arruolato in violazione delle buone pratiche cliniche. Tutti i pazienti hanno ricevuto la terapia farmacologica raccomandata per il decadimento cognitivo.

- **Outcomes primario**

L'outcome primario è stato la valutazione dell'effetto terapeutico di Procognitiv^{R} alla posologia di 2 capsule al giorno, per 30 giorni, utilizzando il test cognitivo standardizzato (MMSE) (Tab. 1).

- **Outcomes secondario**

L'outcome secondario era la valutazione delle variazioni nei principali indici aritmici

cardiovascolari, valutati mediante calcolo del Tpeak-to-Tend (2-3), QT (4), Qtc (5-6) effettuata prima e dopo il trattamento con Procognitiv^{R} alla posologia di 2 capsule al giorno, per 30 giorni, somministrati per via orale, due volte al giorno, per 30 giorni. Il trattamento è stato ben tollerato nella pratica clinica di routine. Tutti i pazienti hanno iniziato il trattamento in studio e nessun soggetto è stato escluso dopo il periodo di run-in (assenza di eventi avversi transitori).

DISCUSSIONE

- **Risultati principali**

È stato osservato un miglioramento statisticamente significativo del valore MMSE (16,857 ± 4,096 vs 17,964 ± 4,138) (con P < 0,001*****) (Tab. 1), dopo 30 giorni di trattamento con Procognitiv^{R} alla posologia di 2 capsule al giorno (Fig. 1) rispetto alla sola terapia standard. L'analisi dei dati dati ha evidenziato variazioni ai limiti della significatività dell'indice aritmico intervallo QT (msec) 441,188 ± 49,021 vs 398,563 ± 43,661 (con P < 0,001 *****) (Tab. 2); QTc Bazzet (msec) (458,375 ± 28,687 vs 412,938 ± 15,648 con P < 0,001*****) (Fig. 2), Fredericia (452,857 ± 29,784 vs 407,625 ± 22,238 con P < 0,001*****) (Fig. 3), Framingham (450,438 ± 30,301 vs 408,500 ± 20,954 con P < 0,001*****) (Fig. 4), Hodges (453,063 ± 29,794 vs 409,000 ± 27,281 con P < 0,001*****) (Fig. 5) e Rautaharju (454,500 ± 28,733 vs 409,313 ± 22,650 P < 0,001*****) (Fig. 6) e indice Tpeak to Tend (msec) 91,313 ± 12,419 vs 89,375 ± 20,759 (con P = 0,781) (Tab. 1), confermando la sicurezza dell'associazione di Procognitiv^{R} nei pazienti anziani. La presenza di variazioni statisticamente significative dell'indice Qtc (Tab. 1) seppur in assenza di variazioni statisticamente significative dell'indice Tp/Te (Tab. 1) rappresenta un vantaggio clinico significativo, perché consente di confermare la sicurezza di Procognitiv^{R} ed un beneficio aggiuntivo, in termini di rischio aritmico, nei pazienti ad alto rischio dovuto a trattamento polifarmacologico e comorbilità.

- **Comparazione con i dati riportati nella letteratura**

In letteratura non sono riportati dati sull'efficacia e sulla sicurezza di Procognitiv^{R} in pazienti

anziani affetti da deterioramento cognitivo. Non esistono studi riguardanti specificamente la valutazione del rischio aritmico (5) su larga scala, in quanto spesso viene adottata solo per pazienti trattati con farmaci per la stabilizzazione comportamentale nelle fasi più avanzate della malattia di Alzheimer. La presenza di modificazioni statisticamente significative dell'indice QT (Fig. 7), QTc (Fig. 8) rappresenta un vantaggio clinico significativo, perché consente di confermare la sicurezza di Procognitiv^{R} ed un beneficio aggiuntivo, in termini di rischio aritmico, nei pazienti ad alto rischio dovuto a trattamento polifarmacologico e comorbilità.

- **Scelte del disegno dello studio**

La scelta del disegno dello studio è legata alla necessità di utilizzare test e variabili standardizzati per effettuare una valutazione scientifica ripetibile e confrontabile. Per questo motivo, è stato scelto il Mini Mental State Examination come test cognitivo standard e l'analisi dell'indice Tpeak-to-Tend (2-3), QT (4), Qtc (5-6) per la valutazione del rischio aritmico.

- Punti di forza e limiti dello studio

- **Punti di forza dello studio**

Lo studio è stato avviato con un numero molto elevato di pazienti arruolati, ed il punto di forza maggiore deriva, quindi, dalla grande significatività dei valori delle variabili misurate prima e dopo il trattamento con Procognitiv^{R} aggiunto alla terapia domiciliare in atto (Tab. 1).

- **Limiti dello studio**

Il limite dello studio è l'osservazione ad un mese di trattamento che, se da un lato mostra la rapidità di azione di Procognitiv^{R}, dall'altro richiede l'elaborazione dei dati di follow-up a medio e lungo termine.

- **Prospettive**

La prospettiva futura è quella di analizzare i dati relativi ad un gruppo di studio ancora più ampio caratterizzato da un periodo di follow-up più lungo (a cadenza di 3 mesi), rispetto alle condizioni basali.

CONCLUSIONI

Lo studio è stato progettato per fornire prove a supporto dell'efficacia di Procognitiv^{R} in 2 somministrazioni giornaliere (150 mg di Omotaurina/die) in aggiunta al trattamento standard per il deterioramento cognitivo nei pazienti anziani. I dati dello studio sottolineano che il trattamento migliora statisticamente il test Mini Mental State Examination (Fig. 1). E' stata riscontrata anche una riduzione statisticamente significativa dell'indice QT corretto per l'età dei soggetti arruolati (QTc) calcolato con l'algoritmo di Bazzet (Fig. 2), Fredericia (Fig. 3), Framingham (Fig. 4), Hodges (Fig. 5) e Rautaharju (Fig. 6). La nostra esperienza ci consente di dichiarare che l'aggiunta del Procognitiv^{R} ai trattamenti farmacologici standard, in pazienti geriatrici con declino cognitivo, deve essere sempre presa in considerazione nei pazienti anziani dato l'effetto positivo evidenziato con il test cognitivo MMSE e la riduzione del rischio aritmico cardiovascolare (Tab. 1).

Contributo degli autori

Prof. Marchitto Nicola per l'ideazione e la progettazione dello studio, l'analisi e l'interpretazione; Prof.ssa Paradiso A. per la collaborazione all'interpretazione dei dati, Dott.ssa Paparello Paola Tamara per l'arruolamento dei pazienti, la valutazione del follow-up tramite MMSE e la registrazione ECG; Dr.ssa Mantuano Chiara per la revisione del manoscritto ed il Prof. Raimondi Gianfranco per l'approvazione finale.

Conflitti di interesse: Gli autori non hanno conflitti di interesse connessi con lo studio.

Aspetti etici: Gli autori certificano che hanno aderito alle linee guida etiche.

Dichiarazione dell'etica umana e consenso alla partecipazione allo studio: Lo studio è stato effettuato nel rispetto delle dichiarazioni sull'etica umana ed il consenso alla partecipazione allo studio.

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COGNITIVE IMPAIRMENT: EFFICACY AND CARDIOVASCULAR SAFETY OF A PRODUCT BASED ON HOMOTAURINA, MICROENCAPSULATED DHA, NADH, SUCROSOMIAL MAGNESIUM, OSSICIAN, VITAMIN B12 (PROCOGNITIV^{R}).

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KEYWORDS: Cognitive impairment, MMSE, Qtc, Tp-Te, Cardiovascular risk.

ABSTRACT

Background: In recent years, nutraceuticals have significantly expanded the therapeutic options available for the treatment of numerous acute and chronic diseases. This aspect has also become evident in the treatment of cognitive decline. The nutraceutical approach currently offers new combination treatment options that improve the cognitive profile and slow down the progression of the disease. International literature also reports reports of increased risk of arrhythmias related to the use of drugs for the treatment of cognitive decline. The main internationally recognized arrhythmic risk indices are the QT index, the Qtc index and the Tpeak-to-Tend index. Only some of these indices are used in clinical practice (QT) while the others are used in scientific research, for the stratification of arrhythmic risk, given the complexity of the assessment. **Aim:** The aim of this study is to evaluate the efficacy and safety of the association of Homotaurine, microencapsulated Dha, Nadh, sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) in association with standard treatment in geriatric patients with cognitive impairment. **Materials and methods:** The present study was designed to investigate the role, in terms of efficacy, using cognitive assessment based on the Mini mental State Examination (MMSE) and safety, by analysis of heart rate variability (HRV) and arrhythmic indices QT, QTc, Tpeak-Tend, of the association of

Homotaurina, microencapsulated DHA, NADH, sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) as an integrative therapy in cognitive decline already in standard treatment. In this study, 343 patients, affected by cognitive decline (mean MMSE 18/30 ± 4) already in standard treatment, were enrolled. Only 341 patients (63 males and 278 females, mean age 77,5 ± 10 years old) complited the follow-up period. During the enrollment period, patients underwent cognitive assessment using the MMSE and non-invasive electrocardiographic recording test, in order to evaluate the arrhythmic risk explored with the analysis of QT, Qtc and Tpeak to Tend Index (Tp/Te). The proposed treatment was Procognitiv 600 mg in two daily doses, for 30 days, added to the standard treatment for cognitive impairment. Data were measured with the cardiolab Xai-medica software and analyzed using the SigmaStat 3.5 software for Windows. **Results:** A statistically significant improvement in the MMSE value (16,857 $\pm$ 4,096 vs 17,964 $\pm$ 4,138 con P < 0,001 *) was observed after 1 month of treatment with Homotaurine, microencapsulated DHA, NADH, Sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) added to the standard treatment for cognitive decline. A borderline statistical significance variation was also observed in arrhytmic index (Table 2). Due to the statistical variability of the QT index, the evaluation of the arrhythmic risk was integrated by calculating the QT corrected for the heart rate of the enrolled subject (Qtc) using the formulas of Bazzet, Fredericia, Framingham, Hodges and Rautaharju. This analysis allowed to highlight statistically significant reductions in Qtc values after 30 days of treatment with normalization of values relative to arrhytmic risk profile (Qtc > 450 msec ♂ and > 480 msec ♀). **Discussion:** The data in Table 1 show that treatment with (Procognitiv^{R}), added to standard treatment, determines a statistically significant increase in mean MMSE score (16,857 $\pm$ 4,096 vs 17,964 $\pm$ 4,138 con P < 0,001 *) in patients with cognitive decline after the first month of treatment. In the international literature, studies are reported that highlight the presence of alterations in neurovegetative modulation with sympathetic hypertonicity mainly during the night and in the early hours of the morning during treatment with anticholinesterase drugs in patients with senile cognitive decline. To the great surprise of our research group, the evaluation of the data relating to arrhytmic index allows us to

underline that the combination therapy with Homotaurine, microencapsulated Dha, Nadh, sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}), added to the standard therapy for cognitive decline, determines a statistically significant reduction in the QTc value evaluated with the formulas of Bazzet (458,375 $\pm$ 28,687 vs 412,938 $\pm$ 15,648 con P < 0,001*) (Fig. 2), Fredericia (452,857 $\pm$ 29,784 vs 407,625 $\pm$ 22,238 con P < 0,001*) (Fig. 3), Framingham (450,438 $\pm$ 30,301 vs 408,500 $\pm$ 20,954 con P < 0,001*) (Fig. 4), Hodges (453,063 $\pm$ 29,794 vs 409,000 $\pm$ 27,281 con P < 0,001*) (Fig. 5) and Rautaharju (454,500 $\pm$ 28,733 vs 409,313 $\pm$ 22,650 P < 0,001*) (Fig. 6), highlighting the safety of the combination treatment (Procognitiv^{R}) in elderly subjects. **Conclusion:** The pilot study we conducted allowed us to highlight, through the evaluation of the MMSE and arrhythmic risk, the synergistic effect of the nutraceutical association (Procognitiv^{R}) in the treatment of senile cognitive decline. Our pilot study allowed us to discover the normalization of cardiovascular arrhythmic risk indices during treatment with (Procognitiv^{R}), added to standard treatment, in contrast to data reported in scientific articles of the international literature regarding sympathetic hypertonicity and therefore increased arrhythmic risk induced by standard treatment or with anticholinesterase drugs. Therefore, on the basis of preliminary data, the role of Procognitiv appears essential to improve the cognitive profile and to reduce the arrhythmic index risk. Since Procognitiv^{R} is a nutraceutical containing multiple active molecules, it is impossible to identify the antiarrhythmic role of the individual active components present in the product or their possible synergistic effect. Currently, the sample under examination was evaluated after the first month of therapy. The data already collected and the analysis of subsequent follow-up data will allow us to extrapolate definitive data on the annual progress of treatment and will allow us to express an evaluation that can be extended to the entire population over 65.

key points

1) Efficacy: In the international scientific literature there are no studies, based on standardized tests, which highlight the efficacy of treatment with the association of Homotaurine, microencapsulated DHA, NADH, sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) in patients affected by cognitive decline.

2) Safety: International literature reports that the administration of some classes of drugs determines an increase in the incidence of major arrhythmias (1). This aspect is particularly important in elderly patients undergoing polypharmacological treatment for cognitive deterioration and other comorbidities as it exposes the patient to a high risk of drug interactions. The final effect of polypharmacological treatments in elderly patients is dose-dependent. It may also be linked to the need to increase the dosage due to worsening of symptoms or tolerance to treatment, with concomitant increase in the risk of life-threatening arrhythmias (1).

why does this paper matter?

Polypharmacological treatment of cognitive decline represents an increasingly emerging clinical condition in relation to the average life expectancy of the population. The risk of arrhythmias is higher in the elderly population subjected to polypharmacological treatment (1). Therefore, it is essential to propose effective and safe pharmacological treatments subjected to an evaluation of the risk of arrhythmia based on scientific evidence (1) in order to minimize, or possibly eliminate, the patient's arrhythmic risk.

INTRODUCTION

Contest

Dementia is an increasingly emerging clinical condition due to the increase in average life expectancy of the population. A systematic review of the literature on the treatment of cognitive decline highlights the pro-arrhythmic and dose-dependent role of some pharmacological treatments that require careful and frequent electrocardiographic follow-up (1). International literature provides several indices

for the assessment of arrhythmic risk. The analysis of Tpeak-to-Tend (2-3), QT (4), Qtc (5-6) indices are used in scientific research for the global stratification of arrhythmia risk (Table 1).

Aim: The present study aims to investigate the role of the association of Homotaurine, microencapsulated DHA, NADH, sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) for the treatment of cognitive decline, evaluated in terms of efficacy and safety (Table 1).

Objective

The aim of this study is to evaluate the effect of the association of Homotaurine, microencapsulated DHA, NADH, sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) explored using the Mini Mental State Examination (MMSE) after 30 days of treatment (Table 1), the safety of the treatment explored by the evaluation of the variability of arrhythmic indices in basal conditions, after 30 days of treatment with the association of Homotaurine, microencapsulated DHA, NADH, sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) (Table 1).

Based on what has been highlighted above, it is increasingly necessary to approach effective and safe pharmacological treatments for the treatment of cognitive decline in elderly patients.

METHODS

Participants and ethical approval

In February 2023, an observational study on the efficacy and safety of the treatment of cognitive decline based on the association of Homotaurine, microencapsulated DHA, NADH, sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) was started at the Department of General Medicine and the Geriatrics Outpatient 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,

performed in basal conditions and after pharmacological treatment with the association of Homotaurine, microencapsulated DHA, NADH, sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) added to standard therapy. Enrollment in the study was voluntary. Patients and caregivers were given informed consent explaining in detail the rationale of the study, the operating methods and the possibility of interrupting the follow-up at any time. Sensitive data were treated in compliance with privacy legislation. The pilot study started in February 2023 and was based on the collection and processing of data from patients at the Geriatrics outpatient clinic of the San Giovanni di Dio Hospital in Fondi (Latina). The study data relate to 343 patients affected by cognitive decline (mean MMSE 18/30 ± 4) already undergoing standard treatment for cognitive impairment. Only 341 patients (63 man and 278 female with mean age 77,5 ± 10 years) complited the follow-up period .

Data collection

All patients enrolled in the study gave their informed consent to the observational study. All patients continued standard pharmacological treatments in compliance with ethical guidelines. Regarding the use of the scale, it was standardized to the international reference system for laboratory tests and instrumental tests. Eligibility requirements for screening included being at least 65 years old. All patients gave written informed consent for data collection. All patients enrolled in the study gave their informed consent to the observational study.

Inclusion and exclusion criteria

The inclusion criteria consider the presence of cognitive impairment assessed with Mini Mental State Examination (MMSE) and an age greater than 65 years. The inclusion criterion required for enrollment is represented by an MMSE value of 18/30 $\pm$ 4, in patients with mild cognitive impairment.

The exclusion criteria are attributable to the electrocardiographic analysis technique of arrhythmic risk that does not allow the

evaluation of patients with rhythm abnormalities or atrial fibrillation. Therefore, the exclusion criteria included treatment with antiarrhythmic drugs and the presence of an Implantable Cardiac Device (ICD) for the possible interference in the assessment of arrhythmic risk compared to the population in sinus rhythm. Patients with difficulties due to functional limitations, with the impossibility of going to the hospital for follow-up, are not included in the study.

Principal exposure variables

The study was designed to evaluate cognitive function using the standardized Mini Mental State Examination (MMSE) test (Table 1). To assess arrhythmic risk, a digital electrocardiographic recording lasting 3 minutes or at least 250 heartbeats was performed. By analyzing the Tpeak-to-Tend (2-3), QT (4), Qtc (5-6) index, it was possible to evaluate the arrhythmic risk before and after pharmacological treatment with the association of Homotaurine, microencapsulated DHA, NADH, Sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) added to standard therapy. (Table 1). Regarding the use of the scale, it was standardized to the international reference system for laboratory tests and instrumental tests.

Covariates

Treatment with antiarrhythmic drugs may alter the electrocardiographic evaluation of arrhythmic indices in patients with chronic heart disease, therefore the electrocardiographic recordings were performed maintaining the standard home treatment, without further increases in dosage, to avoid distortions of heart rate variability and the values of the arrhythmic indices Tpeak-to-Tend (2-3), QT (4), Qtc (5-6).

Outcomes

The expected results of the study are the confirmation of the efficacy on the cognitive aspect of the MMSE of the combination treatment with Homotaurine, microencapsulated DHA, NADH, Sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) added to

the standard therapy and of the safety given by the reduction of the QTc index greater than 450 msec in men and 480 msec in women.

Study design

The study design aimed to analyze cognitive function using the standardized Mini Mental State Examination (MMSE) test. To assess arrhythmic risk, a non-invasive digital electrocardiographic recording was performed for approximately 3 minutes (or 250 heartbeats). Using computerized mathematical algorithms for the calculation of the QT interval, QTc and Tpeak to T end index, it was possible to evaluate the arrhythmic risk before and after pharmacological treatment with the association of Homotaurine, microencapsulated DHA, NADH, Sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) added to standard therapy for cognitive decline. At enrollment, a run-in period was started to subject all enrolled patients to non-invasive 12-lead digital electrocardiographic recording, in order to evaluate the effect of the association of Homotaurine, microencapsulated DHA, NADH, sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) on cardiovascular arrhythmic risk by evaluating Tpeak-to-Tend (2-3), QT (4), Qtc (5-6) index. The three different cardiovascular risk indices were evaluated by electrocardiographic tracing in basal conditions (T0) and after 30 days (T1) of treatment with the association of Homotaurine, microencapsulated DHA, NADH, sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) (Table 1). Treatment is performed using 600 mg capsules in two daily administrations, for 30 days.

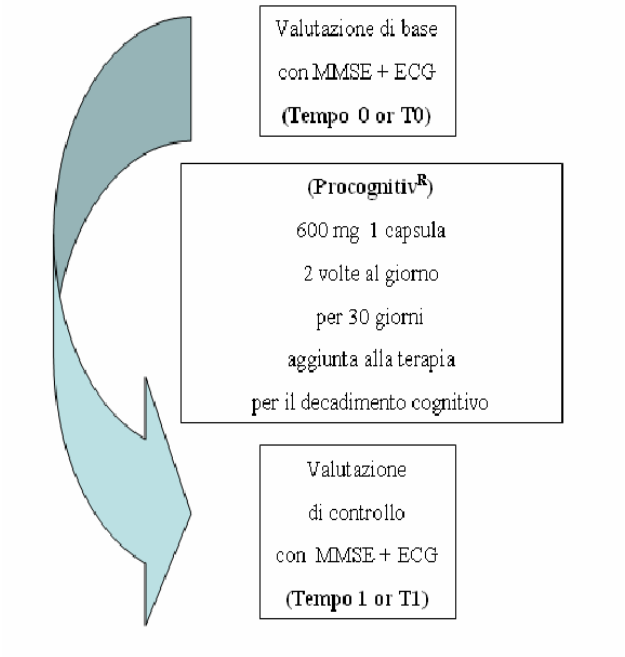
Statistical analysis

Data were measured using Xai-medica cardiolab software and analyzed using SigmaStat 3.5 software for Windows XP. The ANOVA test was used to analyze pre- and post-treatment data recorded in the same subjects enrolled in the study. The ANOVA test allows comparative statistical analyses to be performed in groups of patients > 30 (Table 1). Statistical significance was set at $P < 0.05$.

RESULTS

study flow chart

Baseline evaluation using the MMSE + ECG test (T0) => combination treatment with Homotaurine, microencapsulated DHA, NADH, sucrosomial Magnesium, Oxicyan, Vitamin B12 (Procognitiv^{R}) at a dosage of 600 mg in capsules administered twice a day in addition to standard therapy for cognitive decline => Control re-evaluation after 30 days using the MMSE + ECG test (T1).



Flow chart: Graphic representation of the study design.

Baseline characteristics

As of February 2023, a total of 343 patients start the run-in period but only 341 complited the follow-up period. The mean age of the 341 enrolled patients was 77,5 $\pm$ 10 years. The group of patients who completed the follow-up period consisted of 63 men and 278 women. All enrolled patients have a high cardiovascular risk profile and normal blood pressure (with drug treatment). All patient data meet the study criteria. No patients were randomized in error or enrolled in violation of good clinical practices. Most patients received the recommended drug therapy for chronic hypertension.

Primary Outcomes

The primary outcome was the evaluation of the therapeutic effect of the association of Homotaurine, microencapsulated DHA, NADH, sucrosomial Magnesium, Oxicyan, Vitamin B12 (Procognitiv^{R}) at a dosage of 600 mg administered orally twice a day, for 30 days, using the standardized cognitive test (MMSE) (Tab. 1).

Secondary outcomes

The secondary outcome was the evaluation of changes in the main cardiovascular arrhythmic

indices, assessed by calculation of Tpeak-to-Tend (2-3), QT (4), Qtc (5-6) index performed before and after treatment with the combination of Homotaurine, microencapsulated DHA, NADH, sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) at a dosage of 600 mg administered orally, twice daily, for 30 days. Treatment was well tolerated in routine clinical practice. All patients started study treatment and no subject was excluded after the patient run-in period due to the absence of transient adverse events.

DISCUSSION

Main results

A statistically significant improvement in the MMSE value was observed (16,857 $\pm$ 4,096 vs 17,964 $\pm$ 4,138 con P < 0,001 *****) (Table 1), after 30 days of treatment with the combination of Homotaurine, microencapsulated DHA, NADH, Sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) (Fig. 1). The analysis of the data showed variations bordering on significance in the arrhythmic index QT interval (msec) 441,188 $\pm$ 49,021 + 53.393 vs 398,563 $\pm$ 43,661 (with P P < 0,001*****) (Table 2); QTc Bazzet (msec) (458,375 $\pm$ 28,687 vs 412,938 $\pm$ 15,648 con P < 0,001*****) (Fig. 2), Fredericia (452,857 $\pm$ 29,784 vs 407,625 $\pm$ 22,238 con P < 0,001*****) (Fig. 3), Framingham (450,438 $\pm$ 30,301 vs 408,500 $\pm$ 20,954 con P < 0,001*****) (Fig. 4), Hodges (453,063 $\pm$ 29,794 vs 409,000 $\pm$ 27,281 con P < 0,001*****) (Fig. 5) e Rautaharju (454,500 $\pm$ 28,733 vs 409,313 $\pm$ 22,650 P < 0,001*****) (Fig. 6) and Tpeak to Tend index (msec) 91,313 $\pm$ 12,419 vs 89,375 $\pm$ 20,759 (with P = 0,781) (Table 1), confirming the safety of the association of Homotaurine, microencapsulated DHA, NADH, Sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) in elderly patients. The absence of statistically significant variations in the QT and Tp/Te index (Table 1) and the presence of statistically significant variations in the QTc index (Table 1), which represents a significant clinical advantage, because it allows to confirm the safety of the association of Homotaurine, microencapsulated DHA, NADH, Sucrosomial Magnesium, Oxycian, Vitamin B12

(Procognitiv^{R}) in patients at high arrhythmic risk due to polypharmacological treatment and comorbidity.

comparison with finding reported in the literature

In the literature, there are no data on the efficacy and safety of the combination of Homotaurine, microencapsulated DHA, NADH, sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) in elderly patients with cognitive impairment. There are no studies specifically regarding the evaluation of arrhythmic risk (5) on a large scale, as it is often adopted only for patients treated with drugs for behavioral stabilization in the most advanced stages of Alzheimer's disease. The presence of statistically significant changes in the QT index (Fig. 7), QTc and Tp/Te (Fig. 2-6) represents a significant clinical advantage, because it allows to confirm the safety of the combination of Homotaurine, microencapsulated DHA, NADH, sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) in patients at high arrhythmic risk due to polypharmacological treatment and comorbidity.

study design choices

The choice of study design is linked to the need to use standardized tests and variables to perform a repeatable and comparable scientific assessment. For this reason, the Mini Mental State Examination was chosen as the standard cognitive test and the analysis of the Tpeak-to-Tend (2-3), QT (4), Qtc (5-6) index for the assessment of arrhythmic risk.

- Strengths and limitations of the study

Strengths

The study was started with a large number of enrolled patients, but only 34 completed the follow-up period. The strength of the study is due to the great significance about the values of the variables measured before and after treatment with the combination of Homotaurine, microencapsulated DHA, NADH, sucrosomial Magnesium, Oxicyan, Vitamin B12 (Procognitiv^{R}) (Tab. 1).

Limitations

The limitation of the study is related to the average age of the enrolled patients which does

not allow to generalise the data to the entire elderly population.

Perspectives

The future perspective is to analyze the data relating to a longer follow-up period, to verify the effect of the treatment at 3-6-9-12 months, compared to baseline conditions.

CONCLUSION

The study was designed to provide evidence to support the efficacy of the combination of Homotaurine, microencapsulated DHA, NADH, Sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) 600 mg capsules in 2 daily administrations added to standard treatment for cognitive impairment in elderly patients. The data of the study highlight that the treatment statistically improves the Mini Mental State Examination test (Fig. 1). A statistically significant reduction was found in the QT index corrected for the age of the enrolled subjects (QTc) calculated with the algorithm of Bazzet (Fig. 2), Fredericia (Fig. 3), Framingham (Fig. 4), Hodges (Fig. 5) and Rautaharju (Fig. 6). Our experience allows us to declare that, based on the differences in QTc data re-evaluated after the combination treatment with Homotaurine, microencapsulated DHA, NADH, Sucrosomial Magnesium, Oxycodone, Vitamin B12 (Procognitiv^{R}) 600 mg capsules in 2 daily administrations, for 30 days, in addition to the standard treatment, the addition of the combination with Homotaurine, microencapsulated DHA, NADH, Sucrosomial Magnesium, Oxycian, Vitamin B12 (Procognitiv^{R}) should always be taken into consideration in elderly patients given the positive effect highlighted with the MMSE cognitive test and the reduction of cardiovascular arrhythmic risk (Tab. 1).

Author Contributions

Prof./Dr. Marchitto Nicola for study conception and design, analysis and interpratation; Dr.ssa Paradiso Antonella for collaboration in the interpretation of the data, Dr.ssa Paparello Paola Tamara for the patients enrollment, the evaluation of the follow-up by MMSE and the ECG recording; Dr. Pacella Chiara for the

revision of the manuscript and Prof. Raimondi Gianfranco for the 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.

Acknowledgement: Dott.ssa Marchitto Federica, Dott. De Romanis Fabrizio and Lino Marchitto Paparello for cooperation.

Conflict of Interest: none to declared

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TABLES

	BASE ± DS	CONTROL ± DS	Probability (P)
MMSE (0-30 gg)	16,857 ± 4,096	17,964 ± 4,138	< 0,001 *
Tpeak/Tend	91,313 ± 12,419	89,375 ± 20,759	0,781
QT (msec)	441,188 ± 49,021	398,563 ± 43,661	< 0,001 *
QTc Bazzet (msec)	458,375 ± 28,687	412,938 ± 15,648	< 0,001 *
QTc Fredericia (msec)	452,857 ± 29,784	407,625 ± 22,238	< 0,001 *
QTc Framingham (msec)	450,438 ± 30,301	408,500 ± 20,954	< 0,001 *
QTc Hodges (msec)	453,063 ± 29,794	409,000 ± 27,281	< 0,001 *
Qtc Rautaharju (msec)	454,500 ± 28,733	409,313 ± 22,650	< 0,001 *

Table 1: Descriptive Statistics about MMSE test and Arrhythmic index evaluated before (T0) and after (T1) addictional treatment with Procognitiv^{R} at a dosage of 600 mg orally administered 2 times a day, for 30 days. ANOVA test data are expressed as mean ± Standard Deviation (SD).

FIGURES

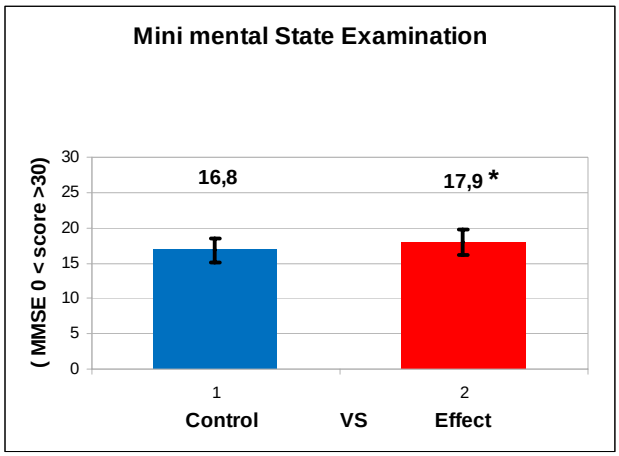

Fig. 1 Graphical representation of the changes in MMSE values before and after additional treatment with Procognitiv. Data expressed as mean +/- Standard Deviation.

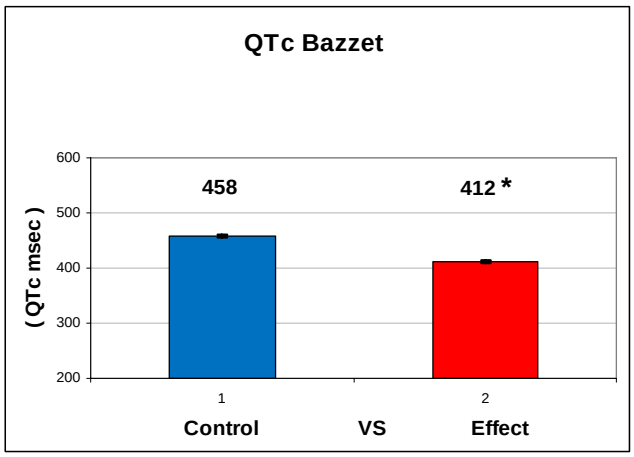

Fig. 2 Graphical representation of the changes in Qtc Bazzet values before and after additional treatment with Procognitiv. Data expressed as mean +/- Standard Deviation.

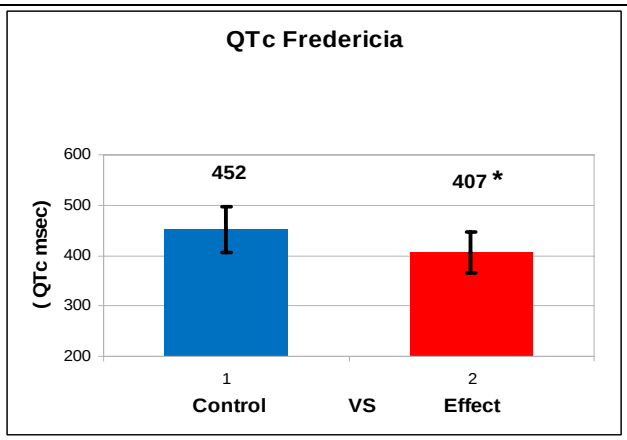

Fig. 3 Graphical representation of the changes in Qtc Framingham values before and after additional treatment with Procognitiv. Data expressed as mean +/- Standard Deviation.

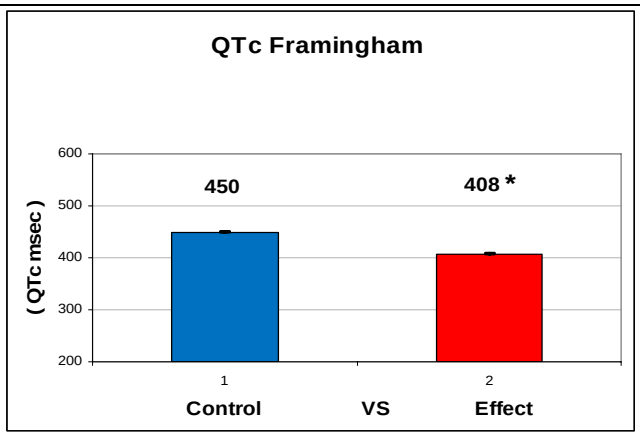

Fig. 4 Graphical representation of the changes in Qtc Fredericia values before and after additional treatment with Procognitiv. Data expressed as mean +/- Standard Deviation.

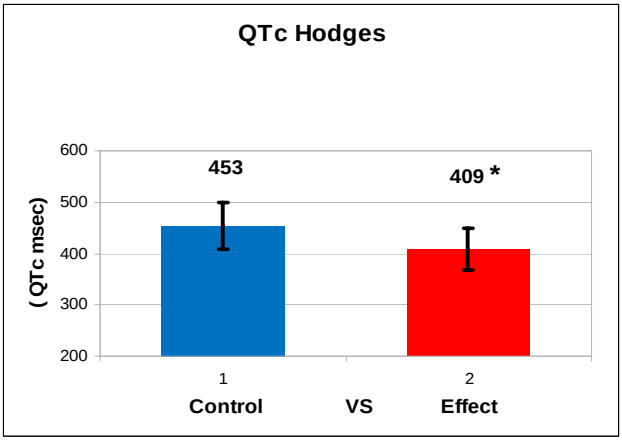

Fig. 5 Graphical representation of the changes in Qtc Hodges values before and after additional treatment with Procognitiv. Data expressed as mean +/- Standard Deviation.

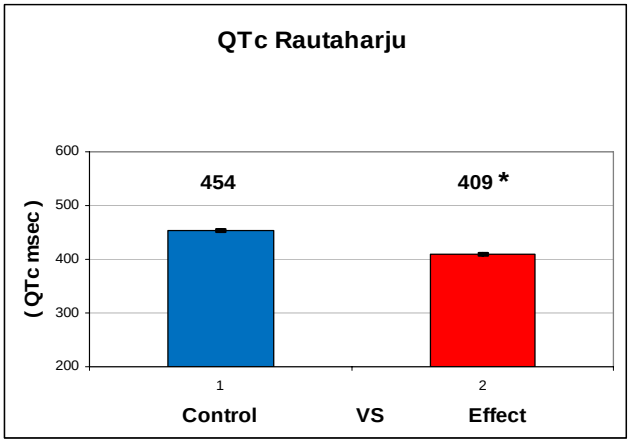

Fig. 6 Graphical representation of the changes in Qtc Rautaharju values before and after additional treatment with Procognitiv. Data expressed as mean +/- Standard Deviation.

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