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Economics of dry needling and botulinum toxin type A for treatment of post-stroke spasticity: a review

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Abstract

Stroke is one of the most common causes of disability and exerts a high burden of direct and indirect costs. Stroke may cause spasticity, which limits patients' abilities and affects their activities of daily living, decreasing their quality of life. Conventional treatments are based on physical therapy, anti-spasticity medication, and botulinum toxin type A (BTX-A). However, recently, non-pharmacological approaches have been used, such as dry needling (DN) of myofascial trigger points. BTX-A and DN are two treatments that aim to decrease spasticity in patients with stroke, but their mode of action, application, and costs differ. Thus, there is a need to determine the comparative economics of post-stroke spasticity treatments. For this purpose, a search for all types of cost-effectiveness studies (randomized controlled trials, matched controls, and cohorts) and models of epidemiological data was performed. Studies were selected if they included economic outcomes in stroke patients treated with BTX-A or DN. As a result, 7 studies of BTX-A and 2 of DN were selected. Similarities were found in the outcomes used to assess the effectiveness of both treatments in most studies, with modifications of the Ashworth Scale [Modified Ashworth Scale (MAS)/Modified Modified Ashworth Scale (MMAS)] and quality-adjusted life year (QALY) being the main indicators of effectiveness. However, both the duration of the studies and the evaluation of costs were highly heterogeneous, making comparison difficult. In conclusion, both BTX-A and DN are cost-effective to treat spasticity in patients with stroke, but there is a need for comparative studies to make direct comparisons of cost-effectiveness with the most frequently used outcomes such as the MMAS and QALYs.

Keywords

Stroke, spasticity, dry needling, botulinum toxin, cost-effectiveness

Introduction

Stroke is a major health problem worldwide and represents one of the most common causes of disability with regard to its impact on functional limitations [1]. In addition, because of the aging population, the absolute number of strokes is expected to increase in the coming years. According to the Global Burden of Disease Study (GBD) [2], the socioeconomic burden of stroke has increased over time, although there has been a decrease in its prevalence [3]. Stroke imposes a high burden in terms of direct and indirect costs. On the one hand, indirect costs occur because of lost productivity due to long-term disability and restricted social functioning leading to a detriment to the patient's quality of life (QoL) as well as premature death [4, 5]. On the other hand, direct costs of care occur resulting from the engagement of health professionals, hospital services [6], medications [7], etc.

Upper motor neuron lesions may result in positive symptoms like spasticity and negative symptoms like weakness or loss of dexterity [8]. Both result in some degree of functional limitation affecting the individual's QoL, as well as somatosensory impairments, also related to activity limitations [9]. Physical therapy treatments can be combined with other pharmacological interventions and/or other medical treatments, such as antispastic drugs or botulinum toxin type A (BTX-A) infiltration. Recently, non-pharmacological approaches have been used, such as dry needling (DN) of myofascial trigger points (MTrPs), which is increasingly used to treat neurological conditions such as stroke [10], Parkinson's disease [11], and multiple sclerosis [12]. Although the reasons for the increase in non-pharmacological treatments such as DN are not clear, the following factors could be relevant: (1) from the patient's perspective, there is a need to shift to more patient-centered treatments, where patients are more involved in decision making about different treatment alternatives; and (2) from the professional and health system perspective, it is important to consider the high costs of pharmacological treatments such as BTX-A infiltration.

BTX-A is the most potent neurotoxin known, and its paralytic effect is due to the blockade of neuromuscular transmission [13]. On the other hand, DN acts by mechanically impairing sensory or motor nerves and dysfunctional motor endplates that contribute to the abnormal functioning of muscular contractile elements [14]. Therefore, the main difference between the two is the mechanism of action, as BTX-A works via chemical denervation while DN induces mechanical damage in the MTrP region [14]. MTrP region (also called Trigger Point Zone, Trigger Spot, or Trigger Area) is understood as "a focus of hyperirritability in a tissue that, when, compressed, is locally tender and, if sufficiently hypersensitive, gives rise to referred pain and tenderness, and sometimes to referred autonomic phenomena and distortion of proprioception" [15]. DN has been also related to pain modulation and has been shown to achieve a washout of sensitizing substances in the MTrP region [16]. DN is considered to be an effective and safe treatment to improve function and spasticity in stroke patients [10, 17, 18] when applied by an experienced physiotherapist. Moreover, although DN may have some adverse effects such as bruising, bleeding, and pain, it does not have the other adverse effects that BTX-A can have in the short and long term. In the short term, the diffusion of toxin from the injected muscle into neighboring muscles may cause undesirable weakness [19] and, depending on the location, this spread can be dangerous and lead to adverse events such as dysphagia, dysarthria, dysphonia, or respiratory compromise [20] amongst others. The long-term adverse effects include chemodenervation leading to muscle atrophy [19]. However, when compared with BTX-A, DN has fewer long-lasting positive effects [14], which requires a greater number of treatment sessions.

Different studies have carried out economic analyses of the aforementioned treatments for post-stroke spasticity. The most studied to date are different variants of botulinum toxin: abobotulinumtoxinA (aboBoNT-A), onabotulinumtoxinA (onaBoNT-A), and incobotulinumtoxinA (incoBoNT-A) [21]. Although recently there have also been secondary analyses of DN clinical trials in patients with subacute [22]

and chronic stroke [23], there are no comparative studies or reviews that have included both of these treatment approaches.

It is important to analyze the clinical effectiveness of both pharmacological and non-pharmacological treatments with respect to their economic impact to inform clinical decision-making. However, only a few studies have been done from this perspective and there exists a great heterogeneity amongst them. Therefore, the objective of this study was to review all the economic publications about DN and BTX-A for post-stroke spasticity.

Methodology

To perform this narrative review, studies were included if they met the following eligibility criteria: 1) involved patients with post-stroke spasticity, with no restrictions regarding race, age, or sex; 2) included an intervention with BTX-A infiltration or DN; 3) reported economic outcomes; 4) consisted of a clinical trial (randomized clinical trial, matched-controls, cohorts) published in a peer-reviewed journal; and 5) written in English or Spanish. Studies were excluded if they met the following criteria: 1) publications that were not specific to the post-stroke population and 2) other types of publications such as book sections, conference abstracts, reviews, or meta-analyses.

Data sources and searches

A search for all types of cost-effectiveness studies was performed on February 15, 2022, without limitations on the dates of publication. The databases consulted to identify studies were PubMed/MEDLINE and Scopus. Three categories of search terms were defined: the first one related to the population (stroke), the second one related to the type of treatment (BTX-A and DN), and the third to the outcome measures (economic). The choice of these search terms was established after a preliminary literature search and keyword identification. The full search strategy was specific to the database in which it was used and the filters applied. In the case of PubMed/Medline, it was "stroke" AND "cost" AND ("botulinum toxin" OR "dry needling") whereas in the case of SCOPUS, it was ("cost-effectiveness" AND "stroke" AND (("botulinum" AND "toxin") OR ("dry" AND "needling"))). Furthermore, reference searching was performed to identify additional studies that the database search might have missed.

Study selection

After a first screening of articles when the title and abstract contained enough information to warrant the study's inclusion, it would progress to the second screening phase, in which the full text of the studies was read, and those that fulfilled all the inclusion criteria were selected.

Results

A total of 9 studies were found (see Table 1). Seven studies analyzed BTX-A infiltration and two studies analyzed DN. No studies compared both interventions.

Table 1. Study characteristics of the included trials

Study	Participants	Intervention	Outcomes	Results	Conclusion
Ward et al. 2005 [24]	The model considered the UK population (58.8 million) Treatment outcome and resource use data were collected from an expert panel experienced in the treatment of post-stroke spasticity	IG: BTX-A injection (first-line) IG: anti-spastic drugs orals and BTX-A injection (second-line) CG: anti-spastic oral drugs	Cost/STM Duration: 1 year	35% of patients receiving oral therapy showed an improvement in pre-treatment functional targets that would warrant continuation of therapy, compared with 73% and 68% of patients treated with BTX-A first- and second-line therapy, respectively The cost/STM was £942 for BTX-A as first-line treatment, £1,387 for BTX-A as second-line treatment, and £1,697 for oral therapy alone	BTX-A is a cost-effective treatment for post-stroke spasticity

Table 1. Study characteristics of the included trials (*continued*)

Study	Participants	Intervention	Outcomes	Results	Conclusion
Shaw et al. 2010 [25]	*n* = 333 adults with upper limb spasticity at the shoulder, elbow, wrist, or hand and reduced upper limb function due to stroke more than 1 month previously IG *n* = 170 CG *n* = 163	IG: BTX-A + 4-week programme of upper limb therapy CG: 4-week programme of upper limb therapy alone	MAS Motricity Index Grip strength ARAT Nine-Hole Peg Test Upper limb basic functional activity questions Barthel ADL Index Stroke Impact Scale EQ-5D Oxford Handicap Scale QALYs Duration: 1, 3, and 12 months	No significant difference in IG *vs.* CG for improved arm function at 1, 3, and 12 months Muscle tone/spasticity at the elbow was decreased in IG *vs.* CG at 1 month. No difference at 3 and 12 months IG improved upper limb muscle strength *vs.* CG at 3 months. No difference at 1 and 12 months *vs.* CG Significant difference IG *vs.* CG for improved specific basic functional activities at 1 and 3 months Significant differences in the IG *vs.* CG for improvement of pain at 12 months 0.36 probability of BTX-A being cost-effective	BTX-A and a 4-week programme of upper limb therapy did not improve upper limb function at 1 month However, improvements were seen in muscle tone, upper limb strength, upper limb functional activities related to undertaking specific basic functional tasks and upper limb pain. The addition of BTX-A to an upper limb therapy programme was not estimated to be cost-effective
Burbaud et al. 2011 [26]	*n* = 870 adults with neurological disease with muscular spasms in relation to dystonia, spasticity, or nerve compression (hemifacial spasm)	BTX-A injection	Latency of effect (in days) SRS Duration of effect (in weeks) Daily cost of BTX-A (ratio of each session's cost to the duration of subjective efficacy) Duration: passed beyond the duration of efficacy (5 months)	The efficacy was significantly greater for facial hemispasm and blepharospasm *vs.* cervical dystonia, and for cervical dystonia *vs.* upper and lower limb spasticity The daily cost of BTX-A injections was higher in cervical dystonia and upper and lower limb spasticity. When associated costs were considered, the daily cost of BTX-A injections was increased	These results show that BTX-A treatment has a low daily cost for a long-lasting effect, with a daily cost/benefit ratio that greatly depends on the indications
Doan et al. 2013 [27]	*n* = 126 Epidemiology, efficacy, and health utilities data were taken from clinical trials done in Scotland on treating upper-limb post-stroke spasticity	IG: usual treatment in Scotland and onaBoNT-A CG: usual treatment in Scotland	EQ-5D QALYs ICER Duration: 1 year	IG improved disability, which translated into greater QALYs but also increased direct medical costs compared with CG. However, the resulting ICER can be considered cost-effective. Moreover, IG can be cost-saving if reduction in caregiver burden was included	In the different scenarios studied, usual treatment in Scotland and BTX-A improved disability at a higher cost than usual treatment
Rychlik et al. 2016 [28]	IG: *n* = 118 adults with upper limb post-stroke spasticity CG: *n* = 110 adults with upper limb post-stroke spasticity	IG: antispastic therapy and incoBoNT-A Two subgroups: IG pretreated and IG naive CG: antispastic therapy (oral antispastic medications, physiotherapy)	Ashworth Scale (AS) DAS SF-12 ICER Duration: visit 1 (baseline visit) and continued visits every 12 weeks (visit 2, 3, 4) until the end of observation (visit 5)	Responder rates of all muscle groups of the upper limbs were significantly higher in the IG than CG Significant differences in favour of the IG for the AS score, the four domains of the DAS, and both dimensions of SF-12—dimensions 'Physical Health' and 'Mental Health' from visit 1 to the end of the study Total health service costs were twice high in IG, however, ICER was consistently superior compared to the CG	Higher responder rates, higher increases in QoL, and superior cost-utility ratios in the BTX-A treatment group underline guideline recommendations for BTX-A treatment in focal or segmental spasticity

Table 1. Study characteristics of the included trials (*continued*)

Study	Participants	Intervention	Outcomes	Results	Conclusion
Lazzaro et al. 2020 [29]	IG: *n* = 864 adults with upper or lower limb post-stroke spasticity CG: *n* = 66 adults with upper or lower limb post-stroke spasticity	IG: rehabilitation + aboBoNT-A CG: rehabilitation only	LYS QALYs ICUR Duration: 2 years	IG costs double compared to CG No difference in LYS IG outperforms CG in terms of QALYs gained ICUR was higher in IG	Rehabilitation + aboBoNT-A is a cost-effective healthcare programme for treating patients with post-stroke spasticity
Fernández Sanchis et al. 2022 [22]	IG: *n* = 40 adults with upper limb hypertonia post-stroke (subacute) CG: *n* = 40 adults with upper limb hypertonia post-stroke (subacute)	IG: normal rehabilitation programme with DN CG: standard rehabilitation programme with neither DN nor a placebo	MMAS EQ-5D QALYs ICER ICUR Duration: baseline visit, 4 weeks, and 8 weeks	Statistically significant improvements were found for QoL in favour of the IG at 4 and 8 weeks IG presented significant improvements according to the MMAS scale at 4 and 8 weeks Based on the rate of responders, the ICER of the IG was very low. Despite the sensitivity analysis performed, the results of the ICUR did not show significant improvements	Cost-effectiveness with responder rate results was favourable for the DN group and was confirmed by the sensitivity analysis according to levels of care. In addition, the results revealed that 4 weeks of treatment could be more cost-effective than 8 weeks
Turcu-Stiolica et al. 2020 [30]	The model was based on a previous study carried out with 218 patients Relevant clinical trials in adults with post-stroke upper limb spasticity	IG: incoBoNT-A CG: conventional therapy programme alone	SF-12 QALY ICER Duration: 3 and 5 years	IG proved to be more effective than CG in the treatment of upper limb post-stroke spasticity according to SF-12 Patients treated with IG had higher costs than CG IG showed a more favourable ICER per QALY gained for both physical and mental health dimensions (ICER €950/QALY)	incoBoNT-A proved to be a more favourable treatment option than conventional therapy programme in the treatment of upper limb post-stroke spasticity, because it is highly cost-effective and improves QoL
Fernández-Sanchis et al. 2022 [23]	IG: *n* = 11 adults with chronic post-stroke hypertonia CG: *n* = 12 adults with chronic post-stroke hypertonia	IG: single-session treatment of DN CG: single-session DN sham intervention	QoL QALYs MMAS ICER Duration: baseline visit and 2 weeks after treatment	Significant differences between groups in terms of QoL two weeks after the intervention in favour of IG Favourable ICER of both €130.14/QALY and < €10/responder for IG MMAS only showed statistically significant improvements in the elbow extensors for the IG	DN is an affordable alternative with good results in the cost-effectiveness analysis—both immediately, and after two weeks of treatment—compared to sham DN in persons with chronic stroke

ADL: Activities of Daily Living; ARAT: Action Research Arm Test; CG: control group; EQ-5D: European QoL-5 Dimensions; ICER: incremental cost-effectiveness ratio; ICUR: incremental cost-utility ratio; IG: intervention group; LYS: life-years saved; MAS: Modified AS; MMAS: Modified MAS; QALY: quality-adjusted life year; DAS: Disability Assessment Scale; SF-12: QoL scale Short Form-12; SRS: Subjective 4-Point Rating Scale; STM: successfully treated months

The most frequent outcomes used in the economic studies and the results of the cost-effectiveness analysis carried out were reviewed. The economic analysis is usually performed through the ICER which is a summary measure representing the economic value of an intervention, compared with an alternative. It is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect), which in the case of the studies selected in this review were specific clinical scales or QALYs.

For the studies that used specific clinical scales, the most commonly used to verify improvements in spasticity and allow direct assessment of the response to treatment were the AS and subsequent modifications of this scale (MAS and MMAS). A prospective multi-centre study compared incoBoNT-A with conventional antispastic treatments for upper limb spasticity after stroke and found more than 56.4% of treatment

responders with incoBoNT-A (*vs.* 26.9% with conventional treatment) after a year [28], with the resulting ICERs favourable to the incoBoNT-A treatment.

Two publications on DN treatment showed similar results with these scales [22, 23]. The first study showed that a single DN session in patients with chronic stroke resulted in statistically significant improvements in elbow extensor spasticity, with 73% of patients responding to the MMAS in the intervention group *vs.* 8% responding in the sham group, considering the values taken before and just after the session with DN [23]. Similarly, in another study on upper limb rehabilitation in patients with subacute stroke that performed DN with the DNHS® technique, an average of 92% of patients responded favourably to the MMAS at 4 weeks *vs.* 18% in the control group, and 70% *vs.* 17% at 8 weeks, with significant differences in elbow flexion, forearm supination, and wrist extension spasticity [22].

In the case of studies that used economic outcomes, the preferred variable for cost-effectiveness analysis was QALYs. This outcome synthesizes the relationship between the number of years of life and the quality, or desirability of health state. In terms of costs, analyses were made from the point of view of society, the health care system, or at the clinic level. A study in Italy comparing treatment with aboBoNT-A and rehabilitation *vs.* rehabilitation alone found an improvement of 0.47 QALY more in the aboBoNT-A group over a 2-year period [29]. However, another study carried out by Doan et al. [27] only found an improvement of 0.107 over 5 years of treatment with usual care and onaBoNT-A. Another study evaluated the cost-effectiveness of treatment with incoBoNT-A *vs.* conventional anti-spasticity treatment using QALY in Romania in 2020 [30] and showed an improvement of more than 1 QALY for the incoBoNT group. In the case of botulinum toxin, some studies found no significant differences compared to rehabilitation alone [25], while for DN significant intra-group differences were found in patients with subacute stroke [22] and inter- and intra-group differences at 2 weeks after a single DN session in patients with chronic stroke [23].

One of the most comprehensive studies was BoTULS 2010 [25]. In this multi-centre study with more than 300 patients, outcomes of upper limb function such as the ARAT, MAS, Barthel ADL Index, troke-related QoL/Stroke Impact Scale, and EQ-5D among others, were observed for one year. Only the QoL data were used for the cost-effectiveness analysis. In the results, we observe the complexity of the cost-effectiveness analysis in this type of treatment as most of the variables show a certain advantage with the use of the toxin. Although there was an improvement in muscle tone in the first month, greater strength after 3 months, and an improvement in pain after 12 months, the authors conclude that "however, these differences were small and of uncertain clinical relevance." BTX-A combined with the upper limb therapy programme indicated that there was only a 0.36 probability of it being cost-effective at a threshold ceiling ratio of 20,000 per QALY [25]. Although the results of the BoTULS study were not very encouraging for the use of the toxin, in 2013, Doan et al. [27] modeled the same data in different scenarios, giving results below the acceptable willingness to pay (established at €20,000/QALY) and even suggesting that savings could be achieved from a societal point of view. Comparing the likelihood of BTX-A being cost-effective with DN treatment, the study carried out by Fernández-Sanchis et al. [23] observed that DN had a 0.5 probability of being cost-effective in terms of QoL with a much lower threshold than BTX-A, and that these results were even more favourable to DN when considering the percentage of responders to the MMAS.

Apart from the aforementioned measures which were the most frequently used, other measures of effectiveness were identified. For example, the STM, which is defined as the percentage of patients who had met or had sufficient improvement in pre-treatment functional targets to warrant continuation of therapy [24], was only used in studies carried out with BTX-A. In the study by Ward et al. [24], the measurement of favourable or unfavourable outcomes to treatments was decided according to the criteria of clinicians participating in a Delphi panel (however, outcomes were based solely on expert opinion and as such may be subject to bias and inaccuracy) with no objective clinical or QoL measures. This cost-effectiveness study of BTX-A *vs.* oral treatment alone for spasticity showed that first-line use of BTX- A resulted in a higher success rate (STM) and lower costs associated with decreased nursing costs. Although nursing hours decreased, physical therapy hours increased, but not at the same level of cost. Moreover, in this review, we found other ways of assessing the efficacy of treatments of spasticity. Burbaud et al. [26] reported an

improvement of 2.4 points with BTX-A on their own 4-point scale SRS in which the patient was simply asked to rate improvement based on a 4-point scale (no, modest, moderate, strong).

Discussion

Some of the cost-effectiveness analyses of BTX-A have been performed on the basis of models whose data came from reviews and network-meta-analyses that, combined with a good decision tree design and a probabilistic sensitivity analysis, give good reliability to the results. However, in other cases, the results of treatment effectiveness were based solely on expert opinion [29]. The use of a Delphi panel to determine the treatment outcome may result in unreliable and irreproducible results. Although the development of models can provide important information and confidence in the analysis, it is necessary to provide a reliable and verifiable source of data so that the results can be trusted.

Both BTX-A and DN studies were based on the same effectiveness outcomes for economic analyses in spasticity, permitting direct comparisons. Both interventions have a good cost-effectiveness ratio compared to placebo or conventional treatments. However, the large differences in cost assessment and treatment duration and lack of a direct comparison between BTX-A and DN make conclusions difficult. A budget impact study in the United Kingdom evaluated the impact of incorporating the new aboBoNT-A *vs.* the established onaBoNT-A and incoBoNT-A, indicating that a 5-year savings of £6,283,829 could be produced [31]. Since improvements in both QoL and responders to the MMAS scale have yielded similar results for the BTX-A and DN studies, it could be expected that the savings, using DN treatment, could be equal to or greater than with BTX-A.

In addition to different costs, there are also different cycle durations in the case of toxins and the number of sessions in DN that affect cost-effectiveness analyses. A study in Australia indicated that treatment with incoBoNT-A could be cost effective beyond 4 cycles per patient in those who were responders to treatment [32]. However, in a DN study, it was observed that a 4-week treatment could be more cost-effective than an 8-week treatment [22]. In another study, in addition to the direct or indirect costs themselves, the increased probability of fractures was related to the use of medication for spasticity such as diazepam or other sleeping pills, indicating that BTX-A can reduce their use and that there would also be a reduction in the costs of surgery and care related to fractures [33].

The diversity of the costs evaluated, the different countries and currencies, and the temporal analysis make it difficult to draw comprehensive conclusions. Moreover, the different protocol applications may also impose cost differences, for example, DN can be included as part of the standardized rehabilitation treatment, without involving any additional costs, or as a specific and complementary treatment as is the case for BTX-A. Apart from the differences derived from this treatment approach, in the case of DN the number of sessions that have the optimal cost-effectiveness has not yet been determined, whereas in the case of BTX-A only one session is needed. The difference in the number of sessions is related to the different mechanism of action whereby its effects last for about 3 months [34]. In the case of patients with subacute stroke, a recent study [22] determined that 4 DN sessions resulted in more cost-effectiveness than 8, but this has not been analyzed in the case of patients with chronic spasticity. Apart from the aforementioned limitations, derived from the heterogeneity of studies and the lack of direct comparisons between the two treatments, there were very few studies of DN. Thus, there is a need for more robust placebo-controlled studies about the effectiveness of DN on spasticity, including more sensitive and specific spasticity outcome measures. Nevertheless, cost-effectiveness studies comparing BTX-A and DN using the most frequently used outcomes such as MMAS and QALYs would be of great interest to allow for a more direct comparative analysis.

Conclusions

Both DN and botulinum toxin treatments present good cost-effectiveness results. However, the appearance of new therapeutic routes requires new studies that compare their efficiency. It is recommended that comparative studies have equivalent durations, effectiveness outcome measures, and a selection of costs from the same perspectives in different health systems.

Abbreviations

aboBoNT-A: abobotulinumtoxinA

AS: Ashworth Scale

BTX-A: botulinum toxin type A

DN: dry needling

EQ-5D: European Quality of Life-5 Dimensions

ICER: incremental cost-effectiveness ratio

incoBoNT-A: incobotulinumtoxinA

MAS: Modified Ashworth Scale

MMAS: Modified Modified Ashworth Scale

MTrPs: myofascial trigger points

onaBoNT-A: onabotulinumtoxinA

QALY: quality-adjusted life year

QoL: quality of life

RCT: randomized controlled trials

STM: successfully treated months

Declarations

Author contributions

DF and PH contributed conception and design of the study; DF and EMGT organized the database and extracted data; DF, EMGT, SC, CR, and CP wrote the first draft of the manuscript; DF, EMGT, PH, and MFL elaborated the final draft. All authors contributed to manuscript revision, read and approved the submitted version.

Conflicts of interest

Pablo Herrero owns the DNHS® trademark.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Data can be requested from the first author by email to efernandez@usj.es.

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