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Case Report

10,000-Fold Effect by a Nitric Oxide Donor (Sodium Nitroprusside) in Essential Tremor Via Intrathecal Superfusion

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Abstract

Essential tremor (ET) is involuntary tremors at upper part of body specially. The pathological neural circuits of GABAergic neuron of cerebellar dentate nucleus, brain stem (locus ceruleans and inferior olives) and thalamus is involved causes tremulous activity within the cerebellothalamocortical circuits. Nitric oxide donors, like Sodium nitroprusside, modulates the antegrade neurotransmission via retrograde neuroregulation by 10000-fold effect. The GABAergic neurons are in turn controlled by the very sensitive 10,000-fold effect circuits via Nitric Oxide. We have utilised intrathecal sodium nitroprusside superfusion (ITSNP) to induce 10000-fold effect after 2 years of failed routine conservative treatment by oral drugs like gabapentin, topiramate, trihexiphenedyl, or other drugs recommended in one ET cases. We have utilised various clinical parameters like spiral drawing (T-CALM TEST) and video recordings of routine daily activities in pre ITSNP and post ITSNP phase.

Keywords: Essential Tremor; 10000-fold Effect; Intrathecal Sodium Nitroprusside

Introduction

Essential tremor (ET) is characterized by involuntary rhythmic and oscillatory movement shaking/tremors in an uncontrolled way at different parts of the body (the hands, arms, head, larynx, tongue, and chin) more in upper part of body then lower, bilateral postural 6 to 12 Hz, followed by a kinetic and resting component. As this is not fatal but this ET causes life hell by not allowing the usual normal functioning of the body. The aetiology in most of the cases is unknown (mostly due to genetics in 50%). The pathological neural circuits of GABAergic neuron of cerebellar dentate nucleus, brain stem (locus ceruleans and inferior olives) and thalamus is involved causes tremulous activity within the cerebellothalamocortical circuits [1].

Nitric oxide donors, like Sodium nitroprusside, modulates the antegrade neurotransmission via retrograde neuroregulation by 10000-fold effect, is well established by the previous authors. The SNP causes release of NOS and then NO which causes 10000-fold effect which modulates the ANT via RNT. Previous authors also postulated the negative effect of NO but those authors had skipped the fact that the SOD and nNOS remains active at synaptic cleft for just 5 to 7 days [2-4].

The GABAergic neurons are in turn controlled by the very sensitive 10,000-fold effect circuits via Nitric Oxide [5,6].

We have utilised this ITSNP to induce 10000-fold effect after 2 years of failed routine conservative treatment by oral drugs like gabapentin, topiramate, trihexiphenedyl, or other drugs recommended in ET cases.

To quantify the effect, we have utilised various clinical parameters like spiral drawing (T-CALM TEST[7]) and video recordings of routine daily activities in pre ITSNP and post ITSNP phase [7].

Case Report

A 42-year-old male presented in normal sensorium in OPD room with chief complaints of bilateral upper limbs symmetrical, involuntary rhythmic and oscillatory movement since SEP 2017, with movements of central body and no movements of head, larynx, tongue and chin. These tremors are relived by the alcoholic ingestion to a small extent. No nasal voice or difficulty in deglutination. No history of head injury, tuberculosis or diabetes. On examination he has full GCS E54V5M6 (GLASGOW COMA SCALE), cranial nerves examination revealed normal 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12th nerve. Motor examination showed bilateral upper limbs, head, central axis body is having tremor in rest and followed by a kinetic and resting component. Muscles have normal nutrition, power and reflexes of upper limbs and lower limbs on both sides. Sensory examination is showing 224/224 (all over body normal ASIA grading) without bladder bowel involvement. ET examination done such as drinking water from a glass, holding arms outstretched, writing and drawing a spiral (T-CALM Essential tremor tests[7]). Archimedean spiral drawings done in pre and post ITSNP phase (Figure 1 and 2).

Figure 1: PREITSNP spiral and handwriting.

Figure 2: POST ITSNP 9th day spiral and handwriting.

MRI of brain stem done which showed normal study in T1, T2 and flair images. MRA was normal.

After well informed written and video consent along with telling all the untoward action (like sweating and apprehension) of ITSNP we superfused ITSNP about 15 ml of the SNP given of 50 mg of SNP dissolved in 200 ml of Dextrose 5% solution with full photoprotection and freshly prepared. Post ITSNP T-CALM ET test done again after 2 hours, 24 hours, 7th day and 9th day with video recordings 95% absence of tremors as told by patient himself.

Discussion

The ET is not a dreadful but slow progressive disease to disturb whole life of the patient [1]. Mostly due to unknown aetiology but a proposed mechanism of ET pathophysiology is via genetic insufficient GABAergic transport [4,5] of cerebellar dentate nucleus, brain stem (locus cerulens and inferior olives), and thalamus. This GABAergic neuron is very much is being in control of 10,000-fold effect [5,6]. The NOD releases NO which causes modulation of GABAergic neuronal circuits via RNT by 10000-fold effect, thus increases the GABA neurotransmitters at synapse in those defective synaptic portions by bypassing the routine ANT impulses which should have activated those GABAnergic vesicles at presynaptic region [2-6].

Pre ITSNP and Post ITSNP T-CALM ET test done with spiral drawing after 2 hours, 24 hours, 7th day and 9th day with video recordings [7] which showed marked recovery as compared from pre ITSNP to post ITSNP 9th day. The daily routine activities like

counting of rupees, drinking water and outstretched both hands showed marked decrease in tremors. As told by the patient himself (with consent) in videos that firstly the central body tremors vanished after 48 hours and then the peripheral tremors after 9th day. This progression of clinical recovery response again signifies and proves the hypothesis that the cerebellothalamocortical circuits was involved from central to peripheral circuits that is from dentate nucleus to thalamus and then cortical region.

From the figure 1 and figure 2 one can really see the significant difference between the handwriting and the Archimedean spiral drawing which is due to the better functioning of GABAergic neural circuits activity within the cerebellothalamocortical circuits.

The 10,000-fold effect is usually being checked by PNAS (Pico Nanosecond Absorption Spectroscopy) [8] but due to absence of this facility in our setup, we were not able to evaluate this modality.

YouTube URLs of PRE ITSNP and POST ITSNP phase is:

PREITSNP essential tremor phase

https://youtu.be/yO7VPuFyscQ

POSTITSNP 24 hrs essential tremor upper limbs movements

https://youtu.be/T9UBNCl4-FE

POSTITSNP 48 hrs essential tremor upper limbs movements

https://youtu.be/zKK7jOCuxwQ

POSTITSNP 72 hrs essential tremor upper limbs movements

https://youtu.be/716L75RszxU

POSTITSNP 96 hrs essential tremor upper limbs movements

https://youtu.be/aThVey9E4ek

POSTITSNP 5th day essential tremor upper limbs movements

https://youtu.be/BgWf1HDvRAQ

POSTITSNP 6th day essential tremor upper limbs movements

https://youtu.be/2uwP1P4AG1g

POSTITSNP 9th day essential tremor upper limbs movements

https://youtu.be/mKtDmvtSFvU

Limitations of the Study

- As this is a pilot study so results are drawn from 1 case only,
- We were not able to evaluate the 10,000-fold effect via pico nanosecond absorption spectroscopy (PNAS) [8].

Conclusion

In chronic non-drug responding Essential tremor after giving ITSNP to induce the 10000-fold effect got 95% improvement on 9th day of post ITSNP phase achieved and in T-CALM test (Archimedean spiral drawings and handwriting) and video recordings. Authors are planning to get more cases for the ITSNP in ET cases.

Disclaimer

No disclaimer for any drug company or patient related matters.

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