



## Original Research Article

## Sub-therapeutic use of botulinum toxin in cervical dystonia, blepharospasm, hemifacial spasm and post herpetic neuralgia during pregnancy : A prospective study

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## ABSTRACT

**Introduction:** We aimed to study sub therapeutic (to reduce intensity of discomfort) and safe dose administration of BoTn/A in certain dystonic neurological movement disorders and Post herpetic Neuralgia (PHN) during pregnancy.

**Materials and Methods:** Total 7 cases studied [(Cervical dystonia =1), (Blepharospasm =2), (Hemi facial spasm=1) and (PHN=3)].

BoTn/A (dysport – SPEYWOOD) was diluted in 10 ml of normal saline. Arbitrary 200 to 500 units was administered depending upon clinical assessment. The patients followed at 1, 3, 4, 12 and 16 weeks. The fetal well being was assessed after delivery and maximum follow-up to 1 and half year period.

Botulinum toxin type a is used as a therapeutic agent in various hyper active movement disorders such as cervical dystonia, blepharospasm, hemi facial spasm and intractable neuropathic pain such as post herpetic neuralgia (PHN).<sup>1</sup> It is an exotoxin produced by clostridium botulinum. It prevents the release of acetylcholine thereby preventing the muscle contraction and reducing pain transmission.

**Result:** The mean age was 35 years. The severity of spasm assessed on intensity, range and frequency of contraction of muscles. In PHN pain intensity measured on VAS score. There was a significant subjective improvement in the spasm in cervical dystonia, blepharo spasm, & hemifacial spasm. The VAS score reduced significantly in all three cases. The fetuses born were healthy and no congenital malformation observed. The children were followed by an average one year were found healthy.

**Conclusion:** We observed that BoTn/A decreased subjective discomfort in Dystonia, spasm and in the intensity of neuropathic pain. It is safer to administer during pregnancy particularly in third trimester as the fetus born were healthy. The oral medications such as antiepileptic are not without side effects. Therefore, we conclude that it is safer to administer during pregnancy particularly in third trimester. However, larger study is needed.

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### 1. Introduction

Botulinum toxin a (BoTn /A) is an exotoxin produced by gram negative bacteria clostridium botulism BoTn /A is a heavy complex protein. Its molecular weight of heavy chain is 100 kDa and of light Chain is 50 kDa. It acts at presynaptic neuromuscular junction and prevents the release of acetylcholine. It paralyzes the muscles and blocks

the transmission of pain impulse. Therefore, it is used in various hyperactive movement disorders<sup>1</sup> and chronic neuropathic pain.<sup>2-4</sup> Its efficacy has been proved in various forms of Dystonia such as cervical (CD), Blepharo spasm, and Hemifacial spasm.<sup>5,6</sup>

In cervical dystonia (CD) there is repeated contraction of sternocleidomastoid and platysma muscle leading to head tilt to one side. Its causes are hereditary metabolic disorder as Wilson's disease, trauma to neck etc. It is not very common.

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In blepharospasm there is arrhythmic contraction of ocular muscles therefore, leading to sudden eyelid closure of both the eyes. It may be due to vision defect, vitamin deficiency, psychological or metabolic disorder. It usually presents in 5<sup>th</sup> decade and female preponderance (2.8:1).

Hemi facial spasm usually present in 5<sup>th</sup> or 6th decade. There is irregular contraction of facial muscles. It may be due to an aberrant artery crossing over the facial nerve or a past history of facial nerve palsy (Bells' palsy). Intracranial tumor is one of the causes which should be ruled out in all cases.

The most common complication of herpes zoster is post herpetic neuralgia (PHN) which can cause chronic and debilitating pain. Post herpetic neuralgia is a condition when pain still persists even after one month of herpetic eruptions. The incidence is seen in approximately 1/20,000 pregnancies.<sup>2</sup> The local peripheral administration of BoTn/A resulting in reduction in various substances that sensitizes nociceptors. The anti-nociceptor effect is associated with the inhibition of release of substance -p and other substances.<sup>7-10</sup>

The symptomatic treatment modalities in dystonia, spasm and neuropathic pain are anticonvulsants drugs such as, Carbamezapine, Gabapentinoids as Pregabalin, Topiramate etc. Administration of BoTn/A injection in general person is one of the most symptomatic therapy favorable. However it is given at 4 to 6 monthly interval, as its effect lasts approximately for 6-8 weeks.<sup>1</sup>

There are few studies of BoTn/A injection use during pregnancy. Due to its large molecular size it does not cross placenta, therefore, it can be preferred during pregnancy in management of Dystonia and PHN.

## 2. Materials and Methods

The study includes 7 cases. Based on the previous trial in two patients of PHN during pregnancy<sup>6</sup> and reviewing the literature<sup>6</sup>, 5 more cases were injected BoTn /a. It is manufactured and marketed as BOTOX 100 units by Allergan and DYSPORT 500 units by Speywood per vial. The efficacy of BOTOX 100 unit is approximately equivalent of 500 units of dysport. Therefore, titration of one brand to other is done accordingly i.e. 1 unit of BO TOX is equivalent of 5 units of DYSPORT. A vial of 500 units of dysport dissolved in 10 ml of normal saline, so to have completely sterile solution ready to be injected. The strength is 5 units per ml. For intramuscular administration 22 or 24 gauge needle is used and for subcutaneous administration insulin syringe. After opening the vial it was used within 6 hours.

A written consent of the patient taken after explaining all possible complications, if any arises during administration and any malformation after delivery to fetus. The average age of patients was 34.84 year ranging from 24 to 42 year. The average gestational age was 29.5 weeks and average

follow up was 10.5 months, ranging from 4 months to 18 months. The dose of dysport varies from 200 units to 500 units (Table 1).

In cervical Dystonia 10 units each was given at three sites in sternocleidomastoid muscle i.e. a total of 300 units. In left hemi facial spasm a total of 200 units injected at three sites dividing as per maximum contracting muscle on clinical examination. In Blepharospasm 150 units at four corners of each eye avoiding elevator palpebrae superioris muscle i.e. a total of 300 units. In PHN as in earlier published two patients 500 units was used<sup>6</sup> in checker board pattern, The new patient included in this study of herpes zoster ophthalmic also received 200 units subcutaneously in similar checker board pattern.

The patients followed at 1, 2, 3, 12 and 16 weeks for the response of BoTn/ A. A maximum 18 months follow up of earlier study treated both the patient<sup>6</sup> was done for their children development.

During administration no untoward side effects were observed, except mild erythematic in two cases of PHN which cleared within few days only.

### 2.1. Brief case history of patients and follows up

Case 1. Thirty four Year female of left cervical dystonia was on irregular administration of BoTn/A injection for 2 years along with Baclofen. After she conceived, she was counseled about future line of treatment. She was advised to discontinue the baclofen and next dose will be administered at 28 weeks of gestation after screening of USG for any fetal malformation. As USG was normal for any fetal malformation, she was injected 300 units of dysport at three sites of right sternocleidomastoid muscle. Her intensity of contraction decreased. She delivered a healthy baby by Caesarian section. APGAR score was 10. The follow up of the child at 4 months was normal.

Case 2 and 3. Thirty four and thirty eight year old patients of blepharospasm were injected total 300 units of dysport equally divides on both side (150 units each side) to reduce the frequency of eye closure. Both patients delivered full term normal child. One patient is still under follow up and child development is normal.

Case 4. Forty year female presented with left hemi facial spasm. She was administered 200 of Dysport in more contracting muscles at three sides. She delivered with Caesarian section a normal child.

Case 5, 6 & 7. Two pregnant patients aged 36 and 38 yr presented in 2017 (published-13) with post herpetic eruptions in thoracic dermatomes and were treated each with 500 units of Dysport. Recently one patient came with PHN in ophthalmic division at 26 weeks of gestation. A total of 200 units of dysport administered at 32 weeks of gestation to reduce pain severity. Patient delivered a healthy baby by caesarian section. None of the patient received A cyclovir (anti viral drug).

**Table 1:** Table showing indication, dose of BoTn-A injection during pregnancy, fetal outcome and period of follow up.

| S. No.  | Age in years | Clinical Indication    | Dose BoTn-A in units (Dysport) | Gestational age in wks | VAS score in PHN <sup>8</sup> * | Mode of Delivery | Outcome of pregnancy | Follow up   |
|---------|--------------|------------------------|--------------------------------|------------------------|---------------------------------|------------------|----------------------|-------------|
| 1       | 24           | Left Cervical dystonia | 300 in units                   | 28                     |                                 | Cs section       | Healthy baby         | 4 months    |
| 2       | 34           | Blepharo spasm         | 300                            | 27                     |                                 | normal           | Healthy baby         | 12 months   |
| 3       | 38           | Blepharo spasm         | 300                            | 28                     |                                 | Normal           | Healthy baby         | 4 months    |
| 4       | 42           | Left Hemi facial spasm | 100                            | 34                     |                                 | normal           | Healthy baby         | 12 months   |
| 5       | 32           | PHN                    | 500                            | 28                     | 9                               | Normal           | Healthy baby         | 18 months   |
| 6       | 36           | PHN                    | 500                            | 32                     | 9                               | Cs Section       | Healthy baby         | 18 months   |
| 7       | 38           | PHN                    | 200                            | 32                     | 8                               | Normal           | Healthy baby         | 6 months    |
| average | (34.84)      |                        |                                | 29.5 wks               |                                 |                  |                      | 10.5 months |

(Software SPSS 15.0 version 9 significant at 0.01 i.e. 1% level of significance)

### 3. Discussion

Treatment of various neurological movement disorders<sup>1,11,12</sup> and intense neuropathic pain involved various non steroidal analgesics, anti epileptic drugs, anti depressants and miscellaneous drugs as a pregabalin etc. Due to their side effects and effect on the fetus is not a welcome approach<sup>11</sup> for treatment. This study aimed to find out a reasonable solution so that intensity and frequency is reduced to a bearable state as well avoid the risk of complications. Based on previous experience and mulling the literature.<sup>9,10,13</sup> the sub therapeutic effect of BoTn/A in certain neurological were studied. This study presents 7 female who received injection of BoTn/A during pregnancy. One patient of cervical dystonia (CD) was already on intramuscular BoTn/A for last 2 years along with baclofen. Two patients of blepharospasm, and one patient of left hemi facial spasm and three patient of PHN were deliberately injected in third trimester to minimize intensity of discomfort during pregnancy and early lactation period. Keeping in mind risk to the pregnancy, course, delivery and fetal outcome and unknown time dependent effects. Use of BoTn/A in pregnancy is considered safe as size of protein is large and it's heavy molecular weight. Therefore, it does not cross the placental barrier and enter systemic circulation.<sup>13</sup> Nevertheless, the study does not aimed curative effect but to achieve cosmetic relief.<sup>8</sup> just to reduce the agony of the patient. Therefore dose of BoTn/A injection was reduced so to avoid any fetal-maternal complications. Encouraged with earlier result<sup>6</sup> and follow up for 18 months of these patient the BoTn/A was injected in some patients of other movement disorders and one new PHN patient. One of the author used small dose (sub-therapeutic) in reducing hyperhidrosis on palm and sole<sup>7</sup> for cosmetic purpose in two patients. It is observed

that there is significant reduction in the contraction of sternocleidomastoid muscle in cervical dystonia, reduction in frequency of contraction in blepharospasm and hemi facial spasm. Similarly, there is reduction in pain intensity in newly included PHN patient of herpes zoster ophthalmicus, as was observed in earlier two published cases of PHN<sup>6</sup> in thoraco-dorsal dermatome distribution.

### 4. Conclusion

It is concluded that BoTn/A could be administered as a sub therapeutic agent in various neurological disorders keeping in mind the side effects of oral medications to outweigh the risk complications and discomfort of oral medications. Therefore, sub-therapeutic dose of BoTn/A can be administered in pregnant women preferably in third trimester for subjective improvement. Nevertheless, further experience of other author and further studied needed.

### 5. Source of funding

None.

### 6. Conflict of interest

None.

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