Management of cervical dystonia with botulinum neurotoxins and EMG/ultrasound guidance

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Abstract

Purpose of review
We provide a practical guide on the use of electromyography (EMG) and ultrasound (US) to assist botulinum neurotoxin (BoNT) treatment in patients with cervical dystonia (CD).

Recent findings
US and EMG guidance improve BoNT treatment in CD. Their use is particularly valuable for targeting deep neck muscles and managing complex cases. There is also evidence that adverse events are reduced when superficial or intermediate layer muscles are injected with assisted guidance.

Summary
A structured clinical approach, based on functional neck anatomy, guides CD assessment and BoNT treatment. Muscles are selected according to clinical, EMG and US findings. US provides anatomical visualization, while EMG complements by detecting muscle activity. We review here the current practice for assisted treatment of CD through BoNT cycles. We also describe how to recognize and manage the main adverse events.

Cervical dystonia (CD) is a challenging condition distinguished by involuntary movements of head, neck and shoulders, often associated with neck pain, that impair daily living activities and reduce quality of life. CD is the most common idiopathic isolated focal dystonia.\(^1\),\(^2\) Thirty years after the first controlled trial, botulinum neurotoxins (BoNT) are currently considered the treatment of choice for CD: recent practice guidelines reported level A or B recommendations for efficacy of different BoNT products in CD.\(^3\) A recent meta-analysis reported that BoNT treatment improves CD, including pain, and subjective perception.\(^4\) However, many practical questions that remained unanswered by evidence-based studies have been addressed by expert consensus.\(^5\),\(^6\)

CD poses specific challenges compared to other dystonia types: (1) the organization of neck muscles is highly redundant allowing to generate a same head/neck movement through variable combinations of muscle activation;\(^7\) (2) multiple joints connect the skull base, the cervical vertebrae and the shoulder girdle, allowing complex articulations in different axial planes; (3) pain is a prominent feature, compared to other focal dystonia syndromes, requiring specific attention; (4) oculocephalic and vestibular reflexes are altered by prolonged abnormal head/neck movements and perception of head and body positioning is impaired.
If BoNT is inappropriately placed, improvement may be insufficient, causing patient dissatisfaction and possible discontinuance of treatment.

Complementary to the traditional approach based on surface anatomy, electromyography (EMG) and ultrasound (US) assistance allow to tailor BoNT treatment to individual needs, to control anatomical and physiologic variables, and to improve efficacy of treatment. There is evidence that EMG and US provide increased accuracy for BoNT injections. They can be usefully combined to detect activity and target posterior neck muscles.

**Muscle selection**

CD patients present remarkably variable combinations of dystonic postures and movements that alter the normal positions of head, neck and shoulders, at rest and during volitional tasks. Abnormal movements often combine head turn, tilt, forward or backward shift, flexion or extension, and shoulder elevation. Treatment is based on BoNT injections into the muscles deemed responsible for the involuntary movements and postures. For example, in rotational CD a classical scheme is based on injecting the ipsilateral splenius capitis and the contralateral sternocleidomastoid or the ipsilateral splenius and levator scapulae combined with the contralateral sternocleidomastoid and trapezius. It has been reckoned that, when a fixed approach based on inspection alone is used, 41% of the overactive muscles would be missed and 25% of the inactive muscles would be inappropriately injected. The reason is that there is insufficient correlation between the phenomenology of CD and muscle involvement, as a variety of combinations of muscle overactivity can give rise to overlapping clinical pictures.

Muscle selection is key for an efficacious treatment. If BoNT is inappropriately placed, improvement may be insufficient, causing patient dissatisfaction and possible discontinuance of treatment. Even when injections are placed into the overactive muscles, however, later changes in the pattern of muscle activation and the development of compensatory muscle activity often require to readjust the injection scheme and to perform more complex reasoning. Overactive dystonic muscles must be distinguished from compensatory muscles.

Dystonic muscles are consistently active in relation to dystonic movements and postures and are primarily responsible for the phenomenology of dystonia. As a consequence of dystonic overactivity, the antagonists may be passively stretched (often causing pain) or may instead actively contract, attempting to compensate. Table 1 lists the redundant organization of cervical muscles controlling head and neck motility. Compensatory muscles are non-primarily dystonic muscles that become activated to correct non-natural postures/movements or to realign gaze. Compensatory muscles may be recruited among a variety of neck muscles: as a rule, they should not be injected, because they are secondarily involved. However, activity of compensatory muscles may persist following BoNT treatment targeted to dystonic muscles, causing abnormal sensorimotor control and joint position errors that can be retrained by physical treatment adjuvant to BoNT injections.

**Patient’s perception**

A support for assessment is provided by the patients. The most distressing symptoms (whether pain, postures, range of motion limitations, etc.) may be annotated and used to guide the decision-making process. Pain is a common reason for seeking treatment in CD and, when related to dystonic muscle overactivity usually improves rapidly after BoNT injections and positively influences the patient’s quality of life. Pain unresponsive to BoNT can instead be related to compensatory muscle activity, joint distress or disc inflammation.

**Clinical examination**

Clinical assessment of CD patients includes inspection and palpation (surface anatomy). At the end of appraisal, a list of candidate muscles actively involved and potentially injectable is prepared (figure 1).

Inspection provides a first-line identification of the disordered motor pattern and orientates on which muscles are potentially involved, particularly by appreciating dystonic postures (tonic component). A baseline orientation is provided by the caput-collum schema of abnormal postures. A “caput” malposition suggests involvement of cervical muscles reaching the base of the skull (figure 2) or the atlas, whereas a “collum” malposition suggests involvement of lower cervical muscles. Frequently there is a combination of both types. The different combinations of dystonic movements and postures can produce variable phenotypes. For the purpose of BoNT injections, we practically distinguish: posture predominant, with few dystonic movements mainly occurring with volitional head repositioning, tremor predominant, with a prevalence of head tremor, jerky and postural, with an equal combination of postures and movements.

The anatomical organization of cervical muscles is shown in table 2. In patients with CD, particularly after some years of disease course, muscle function may be different from normal for 2 main reasons: (1) the lever arms may pivot at different joint angles compared to physiologic action, and (2) voluntary activation may generate an abnormal muscle pattern. For example, the levator scapulae, that normally lifts the ipsilateral shoulder, may tilt the head ipsilaterally if the surrounding
musculature fixes the shoulder or may be responsible for ipsilateral neck rotation. EMG recording and US examination allow to recognize changes compared to normal function.

The patient must be assessed in different conditions: while sitting and standing comfortably, with a preferred head positioning at rest, eyes open and closed (to temporarily abolish influence of visuospatial integration), while voluntarily moving the head back and forth along the 3 axes, and finally using activation and deactivation tasks. Assessment should also include standing, walking naturally and using sensory tricks (or gestes antagonistes).

Neck palpation reveals muscle hypertrophy, evoked pain, and passive range of motion. Muscles located in the superficial layer can be inspected and palpated; muscles in the intermediate layers can only be palpated; deep muscles are inaccessible to physical examination. A limited range of motion may be due to contractures, contraction of contralateral muscles, deficient voluntary activation of cervical muscles or joint limitation. These factors may influence the potential improvement with BoNT and must be considered during the muscle selection procedure.

**Instrumented examination**

EMG and US examinations complement the physical exam and jointly help identifying which muscles are to be selected for injection.

**EMG assessment**

EMG recordings can facilitate recognizing the active muscles, because different muscle combinations may produce a same clinical pattern (table 1). Recordings are performed

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Basic head and neck movement or postures are generated according to a redundant functional anatomical organization of cervical muscles</th>
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<tbody>
<tr>
<td><strong>Action</strong></td>
<td><strong>Bilateral activation</strong></td>
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<tr>
<td><strong>Head extension</strong></td>
<td>Rectus capitis major</td>
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<tr>
<td></td>
<td>Rectus capitis minor</td>
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<tr>
<td></td>
<td>Obliquus capitis superior</td>
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<td>Semispinalis capitis</td>
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<td>Longissimus capitis</td>
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<td>Splenius capitis</td>
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<td></td>
<td>Sternocleidomastoideus</td>
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<td></td>
<td>Trapezius pars descendens</td>
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<tr>
<td><strong>Neck extension</strong></td>
<td>Semispinalis cervicis</td>
</tr>
<tr>
<td></td>
<td>Splenius cervicis</td>
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<tr>
<td></td>
<td>Levator scapulae</td>
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<tr>
<td><strong>Head flexion</strong></td>
<td>Sternocleidomastoideus</td>
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<tr>
<td></td>
<td>Longus capitis</td>
</tr>
<tr>
<td></td>
<td>Rectus capitis anterior</td>
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<tr>
<td><strong>Neck flexion</strong></td>
<td>Scalene anterior</td>
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<tr>
<td></td>
<td>Scalene medius</td>
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<tr>
<td></td>
<td>Scalene posterior</td>
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<tr>
<td></td>
<td>Longus colli</td>
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</table>

| **Action** | **Ipsilateral** | **Contralateral** |
| **Head rotation** | Obliquus capitis inferior | Sternocleidomastoideus |
| | Rectus major | Semispinalis capitis |
| | Splenius capitis | Trapezius (pars descendens) |
| | Longissimus capitis | Longus capitis |
| | Longus colli | |
| **Neck rotation** | Levator scapulae | Semispinalis cervicis |
| | Longissimus cervicis | Scalene anterior |
| | Longus colli | Scalene medius |
| | | Scalene posterior |
| **Lateral head tilt** | Splenius capitis | |
| | Longissimus capitis | |
| | Obliquus capitis superior | |
| | Trapezius (pars descendens) | |
| | Sternocleidomastoideus | |
| | Rectus capitis lateralis | |

This explains the complexity of identifying muscles responsible of dystonic postures and movements solely based on inspection.
on individual muscles or simultaneously on several muscles (polyEMG). Surface and needle electrodes can be combined to simultaneously record several superficial, intermediate and deep layer muscles before performing treatment.

EMG allows to: (1) test activity of non-superficial muscles, which are inaccessible to physical examination; (2) verify whether muscles display tonic, phasic or tremulous activation at rest or during specific tasks; (3) assess and compare activity of antagonist muscles and detect co-activation,15 lack of activation or inappropriate activation.21 The patients can be examined during specific tasks (e.g., while writing, standing or walking) and during active compensatory or inhibiting maneuvers. Combined with clinical assessment, EMG allows to recognize the primarily activated muscles, to be distinguished from those that have a compensatory activation. Selective deactivation of dystonic muscles by a sensory trick can also be detected by EMG.22

**US examination**

US visualizes the neck region of interest at each cervical level. The US probe must have adequate frequency (between 12 and 15 MHz) to provide real time visualization of muscles, connective fasciae and their surroundings. It is useful to combine US anatomical information with functional and EMG findings before drawing-up a final list of candidate muscles.
Measure of muscle size identifies hypertrophy (usually related to dystonic overactivity) or hypotrophy (due to previous BoNT injections or reduced voluntary activation). US echogenicity may be altered by muscle spasm, repeated injections, fibrosis fat or calcifications. US visualizes the muscle surroundings, particularly arteries, veins and nerves, and helps planning a suitable trajectory for injection. Without US, a thin muscle could easily be trespassed or missed. Furthermore, US allows to measure the depth of deep muscles from skin surface and consider the width of subcutaneous tissue (particularly in fat subjects) to calculate the target position. US visualizes muscle contraction during selected movements and unravels anatomical variants. Rhythmic muscle activity synchronous with head tremor can be visualized with US.

Outflow of the solution containing BoNT from needle tip is also visible under US guidance, and its diffusion within the targeted muscles can easily be appreciated (figure 3).

**BoNT injection**

Injections follow muscle selection. Usually few muscles are injected at initial treatment cycles, and more extensive treatment schemes are later implemented, if needed.
The needle tip should reach the muscle belly or be in proximity of the endplate zone. Multiple injections per muscle provide better results than single-point injections. The number of injection points has to be increased in longer multi-segmental muscles, such as the semispinalis capitis or in muscles with more than one belly, like the levator scapulae or the sternocleidomastoid. The trapezius can be injected into different portions (pars descendens, pars trasversalis), depending on which abnormal posture or movement of head or shoulder need to be corrected.

Currently, there are no recommendations on when to use either EMG or US or both, and on which patients. The use of guided injections currently depends on the experience and comfort level of the individual injector. BoNT injections can be made without guidance in the sternocleidomastoid muscle, provided a specific eliciting maneuver is performed (figure 4); however, should side effects occur, US guidance is recommended. For all other cervical muscles precise targeting requires at least one instrumented guide, either EMG or US. A portable EMG device providing acoustic feedback is sufficient to detect muscle overactivity and assist in targeting. This is particularly useful for delivering treatment outside a fully equipped BoNT clinic. Devices combining US and EMG capabilities are also available.

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Figure 3  Muscle ultrasound (US)

US image at C2 level showing the injecting needle with outflow of BoNT solution from needle tip into the splenius capitis muscle (arrow). Superficial, intermediate and deep layers are shown. Distances from surface are reported on the right with 0.5 cm marks, from 0 to 5 cm.

Figure 4  Procedure for a safe approach to injection of the sternocleidomastoid muscle guided by inspection

The head is turned contralaterally by approximately 30°, then the chin is gently pushed down (1); the SCM is pinched with 2 fingers (2) and injected from below tangentially to muscle fibers in the upper third of the muscle belly (3). This approach minimizes BoNT diffusion to the swallowing area and does not necessarily require ultrasound (US) guidance.
possible to inject sub-occipital muscles at C2 level, by inserting a needle nearly 30° posteriorly from the midline: the trapezius pars descendens, the splenius capitis, the semispinalis capitis and the obliquus capitis inferior can be reached along a single track (figure 3). Furthermore, at C3 level, nearly 70° from the posterior midline, with a single penetration the following muscles can be injected: splenius cervicis, levator scapulae, longissimus capitis and multidus. Finally, a needle inserted at C7 level, nearly 45° from midline, may sequentially reach the trapezius, the levator scapulae and the scalenus posterior along the same trajectory (figure 2). There are 2 main groups of deep neck muscles requiring expert management: posteriorly, the sub-occipital muscles, located deep to the semispinalis capitis in proximity of the great occipital nerve, and anteriorly the deep flexor muscles, in proximity of the trachea and vertebrae.

There are 4 sub-occipital muscles: rectus capitis posterior major, rectus capitis posterior minor, obliquus capitis superior, and obliquus capitis inferior. The first 3 extend the head on C1-C2; the rectus capitis major also contributes to the ipsilateral rotation of the head and the obliquus capitis superior additionally tilts the head on a side. The almost horizontal obliquus capitis inferior is inserted on the transverse process of the atlas and originates from the spinous process of epistropheus. This thick muscle rotates the atlanto-axial joint for a narrow angle (nearly 10°): it is a strong headrotator and contributes to head movement related to fast visual exploration.

There are 3 anterior flexor muscles: longus capitis, longus colli (or cervicis), and rectus capitis anterior, which exert a rotatory action if activated unilaterally. The anterior flexor muscles contribute to the “double chin” posture; particularly the longus colli may cause loss of physiologic cervical lordosis. Synergically with them, the rectus capitis lateralis contributes to lateral head tilt. The longus capitis and longus colli can be injected at C5 level with EMG and US guidance by experienced injectors. When hypertrophic, they can alternatively be targeted with a trans-nasal or trans-oral technique using endoscopic inspection.

For head tremor bilateral injections are usually performed in muscles that are active synchronously to tremor. For “no-no” head tremor injections are typically placed bilaterally in the splenius capitis or in the obliquus capitis inferior, depending on EMG recordings. There is limited knowledge regarding “yes-yes” or “round-and-round” head tremors. In the first type, the sternocleidomastoid or the anterior scalene can be targeted; in some head tremors, the levator scapulae and the longissimus capitis can be additionally injected. If there is a clearly recognizable directional preponderance, as in jerky head tremors, muscle selection will take into first account the prevalent direction of pull.

There is no study directly comparing the efficacy and tolerability of different BoNT dilutions in CD. Reconstitution and dilution are performed according to the approved label. More concentrated dilutions may prevent or reduce unwanted diffusion to nearby sites, such as swallowing muscles. Typical dilutions with normal saline solution for CD are: 0.5–2 mL for 100 onabotulinumtoxinA or incobotulinumtoxinA U, 1–2 mL for 500 abobotulinumtoxinA U. Liquid rimabotulinumtoxinB can be injected at the pre-set dilution of 5,000 U/ml.

**Assessment of outcome**

Particularly after the first treatment cycle, but also at later cycles, it is important to rate outcome at time of peak effect (between 4 and 6 weeks after BoNT treatment) using validated rating scales. Two scales were recommended by the International Parkinson and Movement Disorder Society: the CD Impact Scale-S8 and the Toronto Western Spasmodic Torticollis Rating Scale. The same task force also suggested 3 other scales for use in CD: the Tsui scale, the Functional Disability Questionnaire and the Body Concept Scale. Outcome at time of maximal expected efficacy should be compared to the before treatment condition. Videotape recordings are a useful tool for objectively document the patient status; video footage should be structured according to a uniform set of sequences, for example following the dystonia study group videotape protocol.

**Follow-up treatments**

CD is a chronic disease with clinical variability over its course. It has been reckoned that the complexity pattern remains stable in approximately 64% of CD patients under BoNT treatment, while complexity increases or decreases in the remaining 36%. BoNT treatment consists of repeated cycles, with intervals lasting for approximately 12 weeks. Recent evidence suggests that CD patients may be better treated using individually adjusted intervals, keeping a minimum distance between cycles, as indicated on product labels.

Follow-up treatment sessions are influenced by earlier treatment cycles and their outcome. An effective treatment strategy is based on 2 premises: (1) a successful outcome supports repeating the same treatment scheme, (2) refinements are often needed at later cycles. Occasionally, a previous muscle selection strategy needs careful re-planning, particularly when outcome is unsatisfactory, phenomenology changes or pain is prominent. There are no controlled trials addressing treatment strategies when repeated BoNT injection cycles are performed. We
consider that approximately 3 consecutive treatment sessions are necessary before a treatment plan stabilizes. Muscles that become hypotrophic are re-injected with lower doses under US guide (rather than being left without treatment), unless it is considered that they are inactive.

Muscle selection and dosage at follow-up cycles is driven by the same decision-making process. Deep layer muscles are usually added during follow-up assessment, particularly if they were not considered at earlier sessions. Thus, the treatment strategy through cycles can be generally regarded as moving from more superficial to deeper muscle layers. Deeper muscles may also become more active once superficial muscles are inactivated by BoNT.

Management of adverse events

BoNT injections into neck muscles are usually well tolerated. According to a recent meta-analysis, BoNT treatment of CD is associated with an increased risk of 2 adverse events: dysphagia and diffuse weakness/tiredness. Other adverse events, reported with similar prevalence in placebo-treated patients, include: neck weakness, voice changes/hoarseness, sore throat/dry mouth, vertigo/dizziness, malaise/upper respiratory infection, injection site pain and headache. These events are transient, and usually mild or moderate, not requiring specific management. Dysphagia and neck weakness, instead, need special attention, particularly if severe, as they are potentially harmful.

Dysphagia, caused by spread of BoNT to pharyngeal muscles, is a redoubtable side effect particularly if injections are placed in anterior muscles. It occurs from 1 to 10 days after BoNT injection and lasts on average 15.8 days. Iatrogenic dysphagia has to be distinguished from dysphagia associated with CD that is observed independently of BoNT treatment. Experience collected in the pioneering BoNT age indicated that bilateral injections in the sternocleidomastoid muscles are frequently associated with dysphagia. From these observations it became practice to inject in the upper portion of the sternocleidomastoid muscle (figure 4). Alternatively US guidance can be used to reduce the risk of dysphagia. In a recent meta-analysis, the overall incidence of dysphagia has been associated with a risk ratio of 3.04. Dysphagia typically occurs with coarse solids more than liquids; in the affected patients a temporary change to a liquid diet may become necessary.

Conclusion and outlook

Although there is a long tradition of using EMG for performing BoNT injections, the combined use of EMG and US guidance is a recent practice. The available meta-data do not yet recognize its specific safety profile: on the one hand, the increased precision in targeting is considered to reduce adverse events; on the other hand, however, the innovative possibility to target deep neck muscles with EMG and US assistance may potentially lead to an increase of side effects due to proximity of surrounding deep neck structures (such as roots or arteries). EMG- and US-guided injections have impact on visit time and costs. Payers do not normally question EMG or US for BoNT, although there are currently no clear payer policies on the use of guided injections. The efficacy and safety profiles of BoNT in patients with CD have a direct influence on medical decisions, particularly because surgical treatments, such as deep brain stimulation, provide an alternative option. BoNT failure, defined as a less than 30% symptom improvement, has been considered an indication for surgery. The use of EMG and US assistance may improve outcome in patients otherwise poorly responsive to BoNT treatment, who could be addressed to alternative treatment options.

Author contributions

A. Castagna: drafting/revising the manuscript, data acquisition, analysis or interpretation of data. A. Albanese: drafting/revising the manuscript, data acquisition, study concept or design, analysis or interpretation of data, study supervision.

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