EREDETI KÖZLEMÉNY

ORIGINAL ARTICLE

Clinical features of cervical dystonia patients classified by the COL-CAP concept and treated with ultrasound-guided botulinum neurotoxin

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| English | https://doi.org/10.18071/isz.76.0037 | www.elitmed.hu

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Érkezett:
2022. július 5.
Elfogadva:
2022. november 1.

Background and purpose – Cervical dystonia (CD) is the most common form of focal dystonias, where the identification of the involved muscles, the determination of optimal botulinum neurotoxin A (BoNT-A) dose per muscle injection, and precise targeting may be challenging. The aim of the current study is to compare local centre data with international data, enabling the identification of population and methodological factors behind the differences, thereby further improvement of the care of Hungarian patients with CD.

Methods – The data of all consecutive CD patients, who were injected with BoNT-A at the botulinum neurotoxin outpatient clinic at the Department of Neurology, University of Szeged between 11 August and 21 September 2021, were retrospectively collected and analysed in a cross-sectional manner. The frequency of the involved muscles, determined by the application of the collum-caput (COL-CAP) concept, and the parameters for the BoNT-A formulations, injected via ultrasound (US)-guidance, were calculated and compared with available international data.

Results – In the current study, 58 patients (19 males and 39 females) were involved with mean age of 58.4 (± SD 13.6, range 24-81) years. The most common subtype was torticaput (29.3%). Tremor affected 24.1% of patients. The most injected muscles were

Ultrahang-vezérelt botulinum neurotoxin terápiában részesülő COL-CAP módszer szerint klasszifikált cervicalis dystoniás betegek klinikai jellemzői

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Háttér és cél – A cervicalis dystonia (CD) a leggyakoribb fokális dystonia, amelynek esetén az érintett izmok azonosítása, az izmonkénti botulinum neurotoxin A- (BoNT-A-) dózis meghatározása és a precíz injekció kivitelezése egyaránt kihívást jelenthet. A jelen tanulmány célja, hogy a lokáliscentrum-adatokat a nemzetközi adatokkal összehasonlítva azonosítani tudjuk a különbségek hátterében álló populációbeli és metodikai faktorokat, ezáltal javítani tudjuk a CD-ben szenvedő magyar betegek ellátását.

Módszerek – Elvégeztük az összes olyan CD-s beteg retrospektív keresztmetszeti adatfeldolgozását, aki a Szegedi Tudományegyetem Neurológiai Klinikáján 2021. augusztus 11. és szeptember 21. között BoNT-A-oltásban részesült. A collum-caput (COL-CAP) módszerrel meghatározott érintett izmok gyakorisága és az ultrahang- (UH-) vezérelt módon alkalmazott BoNT-A-oltások paraméterei meghatározásra kerültek, majd összehasonlítottuk ezeket a nemzetközi adatokkal.

Eredmények – Ötvennyolc beteget (19 férfi és 39 nő) vontunk be a tanulmányba, átlagéletkoruk 58,4 (± SD 13,6, terjedelem 24–81) év volt. A CD leggyakoribb fő altípusa a torticaput (29,3%) volt. Tremor a betegek 24,1%-át érintette. A leggyakrabban oltott izmok a trapezius (az összes eset 56,9%-a), a levator scapulae (51,7%), a splenius capitis (48,3%), a sternocleidomastoidus (32,8%) és a semispinalis capitis (22,4%) voltak. A bete-

trapezius (56.9% of all cases), followed by the levator scapulae (51.7%), splenius capitis (48.3%), sternocleidomastoid (32.8%), and semispinalis capitis (22.4%). The injected mean doses per patient were 117 ± SD 38.5 (range: 50-180) units for onaBoNT-A, 118 ± SD 29.8 (range: 80-180) units for incoBoNT-A, and 405 ± SD 162 (range: 100-750 units) for aboBoNT-A.
Conclusion – Although there were several similarities between the results of the current and the multicentre studies, all were carried out using the COL-CAP concept and US-guided BoNT-A injections, authors should pay attention to better distinction of torti-forms and the more frequent injection of especially the obliquus capitis inferior, mainly in cases with no-no tremor.

Keywords: cervical dystonia, botulinum neurotoxin, ultrasound, COL-CAP

genként átlagosan injektált dózis onaBoNT-A esetén 117 ± SD 38,5 egység (terjedelem: 50–180) volt, incoBoNT-A esetén 118 ± SD 29,8 egység (terjedelem: 80–180) és aboBoNT-A esetén 405 ± SD 162 egység (terjedelem: 100–750).
Következtetés – Bár a jelenlegi és a multicentrikus tanulmány (mindkettő a COL-CAP koncepciót és UH-vezérelt oltást használt) eredményei között számos hasonlóság adódott, a szerzőknek a jövőben kiemelt figyelmet kell fordítaniuk a torti-formák minél precízebb differenciálására, valamint leginkább az obliquus capitis inferior oltásának gyakoribb alkalmazására, főként a no-no tremorral társuló esetekben.

Kulcsszavak: cervicalis dystonia, botulinum neurotoxin, ultrahang, COL-CAP módszer

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both[1]. Dystonic movements are typically patterned and twisting and may be tremulous. According to body distribution, the most common type is focal dystonia, where only one body region is affected[2]. Cervical dystonia (CD), where the abnormal condition affects the head and neck region, accounts for approximately two thirds of focal dystonias, with an estimated prevalence of 5-50/100.000[2–4]. In addition to the abnormal postures and movements, including tremor as well, the related pain can accompany to the decreased quality of life as well[5]. The pattern of CD is usually complex, making difficult the identification of dystonic muscles.

The collum-caput (COL-CAP) concept was introduced by *Reichel* et al. in 2009 to simplify the recognition of the basic patterns (latero-, ante-, retro- and torticollis; latero-, ante-, retro- and torticaput; lateral shift – the combination of laterocaput to one side and laterocollis to the other side – and sagittal shift – the combination of antecaput and retrocollis or antecollis and retrocaput)[6]. When the affected muscle exerts its major action above the second cervical vertebra, it results in abnormal position of the head, whereas when it is located between the second and seventh cervical vertebrae, it causes the abnormal position of the neck. According to these basic rules, the application of the COL-CAP concept makes considerably easier the selection of muscles to be treated. However, the situation is more complex when dystonic tremor is present. As rule of thumb, based on the dominating pattern of tremor (i.e., no-no or yes-yes) the obliquus capitis inferior (OCI), the sternocleidomastoid, and the splenius capitis may be primarily considered.

The gold standard treatment of CD is botulinum neurotoxin (BoNT)[7, 8]. BoNT acts at cholinergic nerve terminals and inhibits the release of acetylcholine, causing a neuromuscular blocking effect[9]. Primarily A serotypes, including onabotulinumtoxin-A (onaBoNT-A), abobotulinumtoxin-A (aboBoNT-A), and incobotulinumtoxin-A (incoBoNT-A) are applied. These are all demonstrated to be effective on the long term in the treatment of CD with an acceptable side-effect profile[10]. If the dystonic muscles are selected appropriately, the next challenge is the application of the right dose of preparation. Several suggested dose ranges have been published[8, 11, 12]. As a general principle, it is recommended to start the injection with the mostly involved 2-3 muscles using lower doses of the ranges[8].

To improve targeting and to avoid side-effects, device-aided BoNT delivery is widely applied and recommended, especially in complex cases[13–15]. Although electromyography (EMG)-guided injections, utilizing the verification of dystonic activity, may optimize the muscle selection process, the ultrasound (US)-guided technique enables the real-time visualisation of the injection, thereby ensuring not only precise targeting, but the avoidance of unwanted structures, such as vessels and nerves. Available atlases may make easier the standardization of the process[16]. Expert opinions suggest the use of US mainly in the deeply located muscles, but targeting superficial muscles may also be considerably improved by this method[17–19].

Considering the facts detailed above, US-guided (optionally supplemented with EMG recordings) BoNT injections into muscles, selected based on the COL-CAP concept, may be the gold standard method. However, only one multi-centre study reported detailed findings via that technique so far[12, 20]. Accordingly, the aim of the current study is to obtain local centre data to analyse and compare with international data, enabling the identification of differences deriving from the characteristics of patient populations and from methodological issues as well. Especially the latter may help in the implementation of further improvements in the care of our CD patients with their possible extension to the whole Hungarian CD population.

Methods

The data of all consecutive CD patients, who were injected with BoNT-A at the botulinum toxin outpatient clinic at the Department of Neurology, University of Szeged between 11 August and 21 September 2021, were retrospectively collected. All CD patients, included in this retrospective cross-sectional study, were diagnosed by movement disorder specialists following the rational exclusion of possible secondary causes. The pattern of CD was determined by the COL-CAP concept with the identification of components and thereby the probably involved muscles as well. The BoNT-A (ona-, abo-, incoBoNT-A) formulations were applied according to the respective summary of product characteristics following their reconstitution in 2 ml of sterile 0.9 w/v% sodium chloride solution with US-guidance in all patients by physicians trained in its use. In addition to the description of basic demographics, the proportion of tremor and other isolated or combined primary components of CD, the frequency of the involved muscles, and the descriptive statistical parameters for the injected BoNT-A formulations were calculated and compared with available data of an international study[12, 20]. All statistical calculations were performed with the freely available R software (R Development Core Team, https://www.r-project.org/). First, we checked the distribution of data populations with the Shapiro-Wilk test. As the distribution proved to be non-Gaussian in most subdatasets of the applied BoNT-A doses separated according to the injected muscles, or the case number was considerably low, these data were presented as median (and range), but the mean values were also given for better comparison with data of an international study[12, 20], keeping in mind that median values describes the middle of data better. All the other subdatasets showed Gaussian distribution and they were presented as mean ± standard deviation (SD), giving the range as well. In addition to the descriptive statistics detailed above, Fisher's exact test for count data with simulated p-value (based on 2000 replicates) with row-wise post hoc test and with p-value adjustment with the Bonferroni method was applied for the comparison of the frequencies of components determined by the COL-CAP concept and the frequencies of injected muscles in the current and the international study[12, 20]. Furthermore, for association studies regarding COL-CAP components, tremor, and injected muscles, the 'cooccur' function from the 'cooccur' R package was utilized. The obtained p-values for negative or positive associations were adjusted with the Bonferroni method as well. Then the Cramer's V coefficient was determined for those associations which remained significant. The null hypothesis was rejected when the adjusted p-values were < 0.05.

The ethical permission number for this retrospective analysis is 44/2016.

Results

In the current study, 58 patients (19 males and 39 females) were involved with mean age of 58.4 (± SD 13.6, range 24-81) years. The most common components in CD were torticaput and laterocaput (48.3% of all cases, each; mean 13º ± SD 6.2º, range 5-25º, left-sided in 53.6% of cases; mean 14.4º ± SD 9.04º, range 5-50º, right-sided in 57.1% of cases, respectively), retrocaput (37.9%; mean 14.5º ± SD 5.29º, range 7.5-25º), torticollis (31%; mean 32.8º ± SD 19.1º, range 5-75º, right-sided in 66.6% of cases), antecollis (26%; mean 17.1º ± SD 8.53º, range 5-40º), and laterocollis (20.7%; mean 12.2º ± SD 5.07º, range 5-20º, right-sided in 58.3% of cases) according to the COL-CAP concept, neglecting shift forms here. All the other components were present in less than 10% of CD patients **(Figure 1)**. Meaningful positive associations were revealed between torticaput and laterocaput, and torticaput and retrocaput (64.3% and 53.6% co-occurrences, not significant following p-value adjustment; **Figure 2**). Meaningful negative associations were revealed between laterocollis and retrocaput, laterocollis and torticaput, torticollis and retrocaput, torticollis and laterocaput, and torticollis and torticaput **(Figure 2)**. However, only the latter two remained significant following p-value adjustment ($p = 0.002$ and $p < 0.001$, Cramer's V values of 0.462 and 0.634, respectively). If we determine the distribution of main types, putting shift forms into the list as well, the most common form remains torticaput (29.3%), followed by torticollis (25.9%) and laterocaput (13.8%; **Table 1**). All the other main subtypes, including lateral (8.62%) and sagittal shift (5.17%), occurred in less than 10% of CD patients. Regarding the comparison of frequencies of main types in the current and international studies, the difference was remained significant only for torticollis following p-value adjustment (p = 0.01). Combined forms were predominant, involving 2.02 (± SD 0.76) distinct forms on average, not counting the components of shift forms separately, and excluding tremors. Using shift forms instead of components, 27.6% of the patients had only one subtype, 43.1% of patients had two subtypes, whereas 29.3% of patients had three subtypes. The combination of the three most common forms (torticaput, laterocaput and retrocaput) was detected in 17.2% of all cases. If shift forms were separated into their components, pure forms were detected only in 22.4%. Tremor affected 24.1% of patients (no-no tremor: 20.7%, yes-yes tremor: 3.4%). No-no tremor occurred most along with torticaput, laterocaput and retrocaput (75%, 58% and 50% of no-no tremor cases, respectively), whereas 32.1% of torticaput cases were associated with no-no tremor. Meaningful associations were found between no-no tremor and torticaput and laterocaput, but none of them remained significant following p-value adjustment with the Bonferroni method.

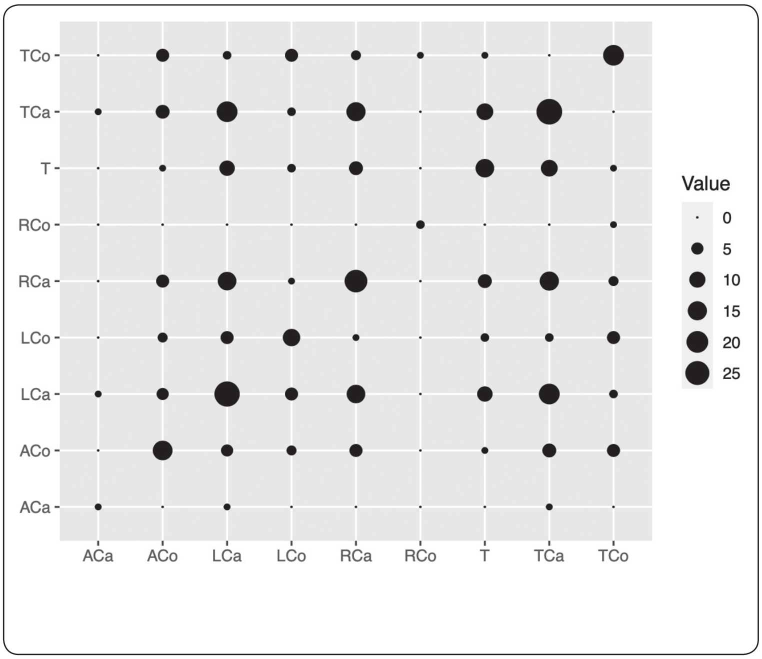

Figure 1. *The counts and associations of COL-CAP components with each other and tremor*

ACa: antecaput, ACo: antecollis, LCa: laterocaput, LCo: laterocollis, RCa: retrocaput, RCo: retrocollis, T: tremor, TCa: torticaput, TCo: torticollis

In the current study, 11 patients were injected with onaBoNT-A (117 ± SD 38.5, range: 50-180 units), 16 patients with incoBoNT-A (118 ± SD 29.8, range: 80-180 units), and 31 patients with aboBoNT-A (405 ± SD 162, range: 100-750 units; **Table 2**). The restrospectively calculated dose conversion ratios for onaBoNT-A:incoBoNT-A:aboBoNT-A (without cross-treatments) were 1:1:3.46. On average, 3.6 (± SD 1.24) muscles were injected per patient. The most injected muscle was the trapezius (56.9% of all cases), followed by the levator scapulae (51.7%), splenius capitis (48.3%), sternocleidomastoid (32.8%), and semispinalis capitis (22.4%; **Table 2**). The frequency of each other injected muscle was less than 20%. Regarding the comparison of frequencies of injected muscles in the current and international studies, the difference was remained significant only for OCI and longissimus capitis following p-value adjustment ($p < 0.001$ and $p = 0.047$, respectively). Considering the dose conversion ratios calculated above, the highest dose (400 units of aboBoNT-A) was injected into the trapezius muscle, whereas the lowest dose (10 units of onaBoNT-A) was injected into the OCI. Regarding the most injected muscles in the three most frequent main subtypes, in torticaput as a main subtype, the sternocleidomastoid (still significant positive association following p-value adjustment, $p < 0.001$, Cramer's V = 0.559) and trapezius in 76.5%, whereas the splenius capitis in 58.8% of cases was injected. In torticollis as a main subtype, the levator

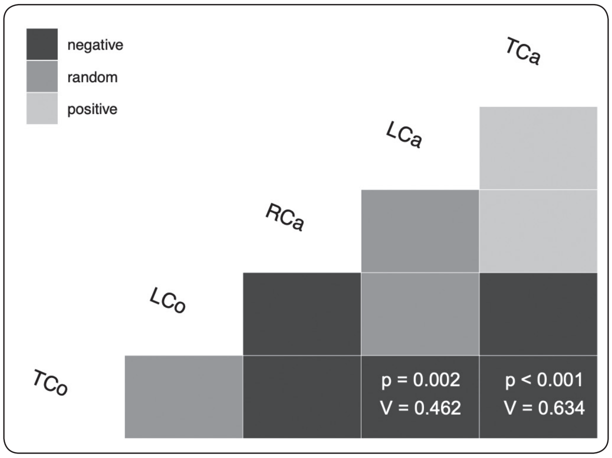

Figure 2. *Meaningful associations of COL-CAP components. Only negative associations between torticollis and laterocaput, and between torticollis and torticaput remained significant following p-value adjustment with the Bonferroni method, and these p-values with corresponding Cramer's V association coefficients are indicated in the figure*

LCa: laterocaput, LCo: laterocollis, RCa: retrocaput, TCa: torticaput, TCo: torticollis scapulae was injected in 73.3% of cases. In laterocaput as a main subtype, the trapezius in 87.5%, whereas the levator scapulae and the semispinalis capitis in 50% of cases were injected. All the other muscles were injected in less than 50% of cases with the three main subtypes.

Discussion

The efficacy of BoNT-A treatment strongly depends on correct muscle and dose selection[21, 22]. Accordingly, the COL-CAP concept, where the muscle selection is guided by the presenting primary subtypes of CD, may considerably help in the component analysis of even complex patterns[23]. Although the original COL-CAP concept does not deal with tremor, recent studies may help in muscle selection in CD cases with tremor[24–26].

The current study demonstrated several similarities and some differences with the results of the multicentre study applying the COL-CAP concept[12, 20]. The demographic parameters (age, gender distribution) were almost the same. The multicentre study did not give the prevalence of each form in the whole patient population; it presented only the distribution of main subtypes. If the forms are not distinguished having primary, secondary, etc., roles, torticaput and laterocaput affect the patients in the same extent (48.3% each), followed by retrocaput and torticollis. If only the main subtypes are considered, torticaput remained the most common in both studies (29.3% in the current vs. 49% in the multicentre study). However, the second most common was torticollis in the current study (25.9% vs. 8.8%), followed by laterocaput (13.8% vs. 16.7%) and retrocaput (8.68% vs. 4.6%). Accordingly, the major difference is that torticaput is underrepresented (but it is still the most frequent form in all contexts), whereas torticollis is significantly overrepresented in the current study. If we put caput and collis torti-forms together, it results in almost the same percentages, i.e., 55.2% in the current and 57.8% in the multicentre study, both higher than demonstrated in the CD PROBE study (47.5%) without applying the COL-CAP concept[27]. So, the difference may derive from the different approach of distinction between caput and collis tortiforms as major subtypes. If the degree of alteration is taken into consideration as well during the distinction process (not presented in the multicentre study), caput forms demonstrated mean degree of alterations from the baseline position between 5-15º (torticaput: 13º), whereas collis forms in between 10-50º (torticollis being the highest with 32.8º). This difference between torticaput and torticollis may be explained by that torticollis may have more potential rotational centres (amongst the second and seventh cervical vertebrae) compared to torticaput. Therefore, as a general principle, the degree of alterations from the baseline larger than 30º should rather raise the suspicion of collis forms as major components, especially when distinguishing between torticaput/-collis and retrocaput/-collis, considering the results of the current study. Another aid during the distinction process between torticaput and torticollis is whether the laryngeal prominence remains in the midline, or not, respectively, which approach was applied in the current study as well. In 23.7% of cases with either dominant torticaput or torticollis, the two alterations were diagnosed together in the multicentre study, whereas this potential combination was not detected in the current study, i.e., there was a strongly significant negative association. The presence of further additional subtypes makes this differentiation difficult, and without the help of EMG, the identification of the torticaput component in addition to torticollis is considerably challenging. Although this may result in the loss of some percentage of torticaput dominant cases, the accompanying predominance of antecollis and laterocollis in our patients with torticollis as the main subtype may further strengthen the neck as site of major involvement. Hence, most of the difference between the studies regarding torti-forms may result from different patient population characteristics as well. Both latero-forms (altogether 15.5% vs. 26.5%) were underrepresented and both retroforms were overrepresented (altogether 12.1% vs. 7.5%) in the current study compared to the multicentre one, but this may rather result from the characteristics of patient populations than diagnostic issues. The frequency of shift forms was similar in both studies (13.8% vs. 14.7% following correction in the multicentre study). Torticaput was most combined with laterocaput and retrocaput in both studies. The average number of distinct forms was lower in the current study (80.5% of the multicentre one), but the authors of the latter one highlighted the diagnostic error in shift detection, which may explain this difference in some extent, as the components of the shift forms were not counted separately in the current study. The proportion of patients having only one subtype was higher in the current study (27.6% vs. 16.3%). If the components of shift forms are counted separately, the frequency of pure forms decreases to 22.4%. The proportion of patients with two or three subtypes was similar in both studies (43.1% vs. 40.2% and 29.3% vs. 24.5%, respectively), and no patient was diagnosed with more than three subtypes in the present study.

The average number of injected muscles was also lower in the current study (85.7% of the multicentre one), probably explained by the higher frequency of pure forms yielding fewer complex cases. Regarding muscle selection for injections in torticaput as a main subtype, sternocleidomastoid, trapezius, and splenius capitis muscles were the most frequently injected ones in both studies (76.5% vs. 84%, 76.5% vs. 60.7%, and 58.8% vs. 88%, respectively). However, there were some differences in the second and third most common subtypes of the current study. The most injected muscle in torticollis as a

Table 1. *Frequency of the main types according to the Collum-Caput (COL-CAP) concept and comparison with international*

Antecaput		Antecollis		Laterocaput		Laterocollis		Retrocaput		Retrocollis	
0%	*1.6%*	3.45%	*2.6%*	13.8%	*16.7%*	1.72%	*9.8%*	8.62%	*4.6%*	3.45%	*2.9%*

The parameters of the multicentre study are presented in italic. **p < 0.01.

Table 2. *Doses and case number distribution regarding the applied botulinum toxins and comparison with international data*[12]

AboBoNT-A	Trap		LS		Scap		SCM		SsCap		SsCer	
Mean	234	*123*	152	*136*	182	*140*	61.1	*118*	138	*111*	100	*102*
SD	108	*47.7*	75	*50.8*	82.1	*47.5*	18.2	*40.1*	46.3	*63.4*	57.7	*73.9*
Median	250	*n.a.*	138	*n.a.*	200	*n.a.*	50.0	*n.a.*	138	*n.a.*	100	*n.a*
MAX	400	*250*	300	*250*	300	*400*	100	*200*	200	*380*	200	*400*
MIN	50	*40*	50	*40*	50	*25*	50	*40*	75	*40*	50	*10*
N	19	*74*	16	*59*	15	*82*	9	*77*	8	*45*	7	*28*
IncoBoNT-A	Trap		LS		Scap		SCM		SsCap		SsCer	
Mean	53.6	*33.0*	52.9	*39.0*	48.6	*36.8*	25	*34.7*	45	*30.7*	63.3	*31.3*
SD	23.4	*13.3*	24.3	*17.9*	20.4	*21.2*	8.36	*15.2*	7.07	*15.2*	11.6	*14.3*
Median	50	*n.a.*	60	*n.a.*	50	*n.a.*	20	*n.a.*	45	*n.a.*	70	*n.a.*
MAX	100	*60*	80	*80*	90	*100*	40	*70*	50	*70*	70	*50*
MIN	30	*10*	20	*10*	30	*10*	20	*15*	40	*10*	50	*10*
N	11	*35*	7	*34*	7	*43*	6	*43*	2	*15*	3	*8*
OnaBoNT-A	Trap		LS		Scap		SCM		SsCap		SsCer	
Mean	40	*29.2*	51.4	*32.8*	61.7	*49.2*	25	*40.8*	70	*19.7*	100	*18*
SD	20	*13.2*	13.5	*12.3*	26.4	*26.0*	5.77	*15.5*	17.3	*13.2*	0	*8.50*
Median	40	*n.a.*	50	*n.a.*	65	*n.a.*	25	*n.a.*	80	*n.a.*	100	*n.a.*
MAX	60	*100*	70	*70*	100	*130*	30	*80*	80	*100*	100	*40*
MIN	20	*10*	40	*10*	20	*10*	20	*7.5*	50	*7.5*	100	*5*
N	3	*73*	7	*59*	6	*134*	4	*125*	3	*59*	1	*37*
Total	Trap		LS		Scap		SCM		SsCap		SsCer	
N	33	*182*	30	*152*	28	*259*	19	*245*	13	*119*	11	*73*
Proportion (%)	56.9	*59.7*	51.7	*49.8*	48.3	*84.9*	32.8	*80.3*	22.4	*39.0*	19	*23.9*

AboBoNT-A: abobotulinumtoxin-A, IncoBoNT-A: incobotulinumtoxin-A, LS: levator scapulae, Long: longissimus capitis, MAX: maximum, MIN: inferior, OnaBoNT-A: onabotulinumtoxin-A, Scap: splenius capitis, SCM: sternocleidomastoid, SD: standard deviation, Scer: splenius cervicis, scalene, Trap: trapezius. The parameters of the multicentre study are presented in italic. *p < 0.05, ***p < 0.001.

main subtype was levator scapulae in the current study, whereas splenius capitis in the multicentre study. In case of laterocaput as a main subtype, trapezius was the most injected followed by levator scapulae in the current study, whereas splenius capitis was the most injected muscle in the multicentre study, followed by levator scapulae and trapezius. Dystonic activity of levator scapulae is capable of causing alterations in caput and collum levels as well, in light of the origin of its fibres. The major difference regarding the frequency of injected muscles in the two *data*[20]

Torticaput		Torticollis**		Shift (Lateral + Saggital)	
29.3%	*49%*	25.9%	*8.8%*	8.62% + 5.17%	*3.9%*

Scer		SM		OCI		Long	
150	*75.4*	150	*87.5*	0	*117*	0	*87.3*
0	*47.5*	0	*36.8*	0	*43.6*	0	*35.7*
150	*n.a.*	150	*n.a.*	0	*n.a.*	0	*n.a.*
150	*200*	150	*175*	0	*200*	0	*160*
150	*25*	150	*20*	0	*40*	0	*25*
3	*11*	1	*18*	0	*44*	0	*15*
Scer		SM		OCI		Long	
43.3	*65*	20	*28.8*	0	*31.7*	0	*27*
20.8	*49.5*	0	*16.5*	0	*20.9*	0	*10.6*
50	*n.a.*	20	*n.a.*	0	*n.a.*	0	*n.a.*
60	*100*	20	*50*	0	*90*	0	*40*
20	*30*	20	*10*	0	*5*	0	*10*
3	*2*	1	*4*	0	*23*	0	*10*
Scer		SM		OCI		Long	
0	*13.3*	20	*24.3*	10	*20.6*	0	*20.5*
0	*4.80*	0	*5.80*	0	*11.4*	0	*9.90*
0	*n.a.*	20	*n.a.*	10	*n.a.*	0	*n.a.*
0	*20*	20	*30*	10	*50*	0	*40*
0	*5*	20	*10*	10	*7.5*	0	*5*
0	*9*	1	*14*	1	*45*	0	*27*
Scer		SM		OCI***		Long*	
6	*22*	3	*36*	1	*112*	0	*52*
10.3	*7.21*	5.17	*11.8*	1.72	*36.7*	0	*17.1*

minimum, N: case number, n.a.: not available, OCI: obliquus capitis
SsCap: semispinalis capitis, SsCer: semispinalis cervicis, SM: middle

studies was the higher proportion of splenius capitis in the multicentre study (48.3% vs. 84.9%). Furthermore, the proportion of sternocleidomastoid injection was also higher in the multicentre study (32.8% vs. 80.3%). The injection proportion of the other two out of five most injected muscles were similar in the two studies; trapezius: 56.9% vs. 59.7%, levator scapulae: 51.7% vs. 49.8%. Regarding the fifth most injected muscle in both studies, the frequency of the injection of semispinalis capitis was merely the half in the current study compared to the multicentre one (22.4% vs. 39%). The difference in main subtype frequencies detailed above may only partially explain the considerably larger proportion of splenius capitis and sternocleidomastoid injections in the multicentre study. Another study involving 200 consecutive CD cases not classified according to the COL-CAP concept, but with similar demographic parameters to the current and multicentre studies, demonstrated that trapezius muscle was the most commonly injected one similar to the current work, followed by splenius capitis, sternocleidomastoid and levator scapulae, but for historical reasons, they included some nuchal paravertebral muscles as well to the trapezius group[11]. Some parts of differences in the proportion of the injected muscles may be explained by different tremor frequencies in the current and multicentre studies (24.1% vs. 55.6%), most commonly occurring along with the presence of torticaput (75% vs. 57.3% of cases), and less commonly observed with collis forms[25]. Tremor is an important accompanying feature of varying, but usually substantial proportion (14-86.6%) of CD cases[25]. Historically, the most frequently injected muscles in dystonic head tremor are splenius capitis and sternocleidomastoid, without appropriate evidence[28]. Only if distribution of muscle injections were taken into account, bilateral splenius capitis, sternocleidomastoid, OCI and trapezius injections were significantly more frequent in patients with dystonic head tremor compared to those without it[25].

The application of EMG may considerably help in the identification of affected muscles in dystonic head tremor. *Schramm* et al. assessed the involvement of only splenius capitis and OCI in 35 CD patients with dystonic no-no head tremor[24]. They demonstrated that burst-like tremor activity was present in bilateral OCI in 71.4%, in unilateral splenius capitis in 51.4%, whereas in unilateral OCI in 28.5%, and in bilateral splenius capitis in only 5.7% of cases. A recent single-photon emission computed tomography study demonstrated that in no-no dystonic head tremor, the most involved muscle was OCI (78.3%, in 52.2% of cases with bilateral involvement) and sternocleidomastoid (78.3%, in 47.8% of cases with bilateral involvement), followed by splenius capitis (69.6%, in 26% of cases with bilateral involvement)[26]. In line with the results of the above EMG and imaging studies, the injection frequency of OCI was significantly higher in the multicentre study compared to the current one, both studies lacking the use of EMG in most cases. Although the authors of the current study regularly apply OCI injection as well (but at low frequency yet), only one OCI injection was documented in the current cross-sectional analyses, which may underrepresent the average 3-4 OCI injection cases per session. Although the injection of OCI would be desirable in a substantial number of cases with torticaput and/or no-no tremor, it needs great expertise even under US control[26]. Great care should be taken during the injection of this deeply located muscle, as it is small and the greater occipital nerve, the vertebral artery, and the cerebrospinal fluid space are close. Therefore, if the needle is not handled appropriately, the adjacent structures may be erroneously injected or damaged. The frequency of longissimus capitis injection was also significantly lower in the current study compared to the multicentre one.

The mean total doses for treatment sessions were lower in the current study (onaBoNT-A: 73.4%, incoBoNT-A: 68.1%, aboBoNT-A: 62.1% of the multicentre study). Furthermore, the study mentioned above from a reference centre with a minimum of economic or legal restriction regarding BoNT-A therapy applied onaBoNT-A and incoBoNT-A at a mean dose of 262.6 unit[11]. Their patients were injected based on only palpation and anatomical landmarks, without guidance techniques. It is important as precision injection may considerably decrease the effective dose[12]. However, except sternocleidomastoid, where the current study applied lower doses, another long-term open study in the pre-COL-CAP era with aboBoNT-A by *Bentivoglio* et al. demonstrated similar mean doses and ranges for trapezius, scalenus medius, splenius capitis and levator scapulae[29]. Nevertheless, almost all the applied injections in the current study were within the range given by the experts[8]. Regarding the applied doses in the most injected five muscles, trapezius was injected with considerably higher, and sternocleidomastoid was injected with considerably lower doses in the current study compared to the multicentre one. The other three muscles were injected with similar doses. Approximately half of the difference could be explained by the lower average number of injected muscles in the current study, and the higher frequency of sternocleidomastoid injection in the multicentre study may also explain some percentage of the remaining difference. The retrospectively calculated dose conversion ratios (without cross-treatments) for the above three products were similar, i.e., 1:1:3.46 in the current study, and 1:1.08:4.09 in the multicentre study. Regarding aboBoNT-A, they are both higher than the recommended 1:1:3 or 1:1:2.5, based on data obtained from previous studies[10]. However, there was not a seemingly higher frequency of adverse events in the aboBoNT-A group.

In conclusion, there were several similarities between the results of the current and the multicentre studies, both carried out using the COL-CAP concept and US-guided BoNT-A injections in all patients. Based on the results of the current study, the impressions of the authors are that further improvements are needed in muscle identification mainly in complex torti-forms, which could be most easily implemented by the utilization of EMG in that patient population, and furthermore, with improving expertise, the injection of longissimus capitis, and especially OCI should be more commonly applied, that latter particularly in patients with no-no tremor. Although the muscles for injections can be well selected based on the COL-CAP concept and guiding techniques, the determination of the ideal dose per muscle needs individual dose titration within the predefined, usually wide ranges.

ACKNOWLEDGEMENT – András Salamon was supported by the ‘National Talent Programme’ (NTP-NFTÖ-21-B-0100).

Irodalom

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