

Botulinum Toxin-A use in Paediatric Hypertonia: Canadian Practice Patterns

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ABSTRACT: Background: This study aims to assess current practices of Canadian physicians providing botulinum toxin-A (BoNT-A) treatments for children with hypertonia and to contrast these with international “best practice” recommendations, in order to identify practice variability and opportunities for knowledge translation. **Methods:** Thirteen Canadian physicians assembled to develop and analyze results of a cross-sectional electronic survey, sent to 50 physicians across Canada. **Results:** Seventy-eight percent (39/50) of physicians completed the survey. The most frequently identified assessment tools were Gross Motor Function Classification System, Modified Tardieu Scale and neurological examination. Goal-setting tools were infrequently utilized. Common indications for BoNT-A injections and the muscles injected were identified. Significant variability was identified in using BoNT-A for hip displacement associated with hypertonia. The most frequent adverse event reported was localized weakness; 54% reporting this “occasionally” and 15% “frequently”. Generalized weakness, fatigue, ptosis, diplopia, dysphagia, aspiration, respiratory distress, dysphonia and urinary incontinence were reported rarely or never. For dosage, 52% identified 16 Units/kg body weight of Botox® as maximum. A majority (64%) reported a maximum 400 Units for injection at one time. For localization, electrical stimulation and ultrasound were used infrequently (38% and 19% respectively). Distraction was the most frequently used pain-management technique (64%). **Conclusions:** Canadian physicians generally adhere to international best practices when using BoNT-A to treat paediatric hypertonia. Two knowledge-translation opportunities were identified: use of individualized goal setting prior to BoNT-A and enhancing localization techniques. Physicians reported a good safety profile of BoNT-A in children.

RÉSUMÉ: Utilisation de la toxine botulique A dans l'hypertonie chez l'enfant : modalités de pratique au Canada. Contexte : Le but de cette étude était d'évaluer les pratiques actuelles des médecins Canadiens qui traitent des enfants atteints d'hypertonie au moyen de la toxine botulique A (BoNT-A) et de les comparer aux recommandations internationales de pratiques exemplaires afin d'identifier la variabilité dans les pratiques et les possibilités de transfert de connaissances. **Méthode :** Treize médecins Canadiens se sont réunis afin de d'élaborer et d'analyser les résultats d'une enquête électronique transversale auprès de 50 médecins à travers le Canada. **Résultats :** Soixante-dix-sept pour cent (39/50) médecins ont complété l'enquête. Les outils d'évaluation les plus fréquemment identifiés étaient le système de classification de la fonction motrice globale (GMFCS), l'échelle modifiée de Tardieu et l'examen neurologique. Les outils pour la définition d'objectifs étaient peu utilisés. Les indications les plus fréquentes des injections de BoNT-A et les muscles ciblés ont été identifiés. Il existe une importante variabilité en ce qui concerne l'utilisation de la BoNT-A pour une luxation de la hanche associée à l'hypertonie. L'incident thérapeutique le plus souvent rapporté était une faiblesse localisée, qui était rapportée « occasionnellement » par 54% des répondants et « fréquemment » par 15% d'entre eux. Les symptômes suivants étaient rarement ou jamais rapportés : faiblesse généralisée, fatigue, ptose, diplopie, dysphagie, aspiration, détresse respiratoire, dysphonie et incontinence urinaire. Quant au dosage, 52% ont indiqué que 16 unités/kg était la dose maximum de Botox® utilisée. La majorité des médecins (64%) ont rapporté la dose de 400 unités comme étant la dose maximale en un même traitement. La stimulation électrique et l'ultrasonographie étaient rarement utilisées (38% et 19% respectivement) pour la localisation. La distraction était la technique de gestion de la douleur la plus fréquemment utilisée (64%). **Conclusions :** Les médecins Canadiens adhèrent généralement aux pratiques exemplaires internationales quand ils utilisent la BoNT-A pour traiter l'hypertonie chez l'enfant. Ils pourraient bénéficier d'un transfert de connaissances sur les sujets suivants : la définition d'objectifs individualisés avant le traitement et l'amélioration des techniques de localisation. Les médecins ont rapporté que le profil de sécurité de la BoNT-A chez les enfants était bon.

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Intramuscular injections of Botulinum Toxin A (BoNT-A) produce a local, reversible neuromuscular blockade causing a reduction in neurologically mediated hypertonia (spasticity or dystonia)¹. Botulinum toxin-A has been shown to be an effective intervention in the management of upper and lower limb hypertonia in children². Botulinum toxin-A is most often used for children with cerebral palsy (CP) or acquired brain injury.

In 2008, Health Canada issued an advisory cautioning health care providers about potential safety risks of botulinum toxins³. The focus of this communication was the potential for distant

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Table 1: Physician use of baseline assessment tools

	Assessment Tool	Physicians Reporting Routine Use (%)
Hypertonia Subtype	Neurological Examination	91%
	Hypertonia Assessment Tool (HAT)	15%
Hypertonia Severity	Modified Tardieu Scale (MTS)	72%
	Modified Ashworth Scale (MAS)	62%
Passive Range of Motion	MTS without goniometry	75%
	Goniometry	38%
	MTS with goniometry	34%
Overall Function	Gross Motor Function Classification System (GMFCS)	88%
	Manual Ability Classification System (MACS)	28%
Impact of Hypertonia on Upper Limb (UL) Function	Informal evaluation	97%
Impact of Hypertonia on Lower Limb (LL) Function	(Observational) video gait analysis	50%
	Gross Motor Function Measure (GMFM)	40%
	Functional Mobility Scale (FMS)	37%
	Standardized observational gait scale	30%
	3-D instrumented video gait analysis	24%
	Functional Independence Measure for Children (WeeFIM)	17%
Occupational Performance and Potential Goals of BoNT-A Therapy	Goal Attainment Scale (GAS)	28%

Tests used <10% of the time included: Australian Spasticity Assessment Scale (ASAS), Barry Albright Dystonia (BADJ), Quality of Upper Extremities Skills Test (QUEST) Assisting Hand Assessment (AHA), 3-D instrumented motion analysis, Melbourne Assessment of Upper Limb Function (MAULF), Paediatric Evaluation of Disability Inventory (PEDI), Canadian Occupational Performance Measure (COPM)

toxin spread in children with neurologic conditions such as CP. Associated with these warnings, physicians have sought information related to BoNT-A in children such as dosing, types and frequency of side effects and methods of localizing muscles for injections.

Two international consensus statements and a European consensus statement representing “best practice” have recently been published to guide physicians on the practical use of BoNT-A in children with hypertonia⁴⁻⁶. Recommendations were provided based on a systematic review of available evidence and expert opinion. The aim of this study is to assess current practices of Canadian physicians providing BoNT-A treatments for children with hypertonia in relation to these “best practice” recommendations. We aim to identify areas where there is variability in Canadian practice and identify areas for knowledge translation activities related to BoNT-A use in children/youth. The overall goal of the project is to optimize the use of BoNT-A as an adjunctive therapy within comprehensive rehabilitation programs for Canadian children with hypertonia.

METHODS

Physician Panel

A panel of 13 Canadian physicians was formed, comprised of neurologists, physiatrists, orthopedic surgeons and developmental paediatricians who use BoNT-A in paediatric hypertonia. The panel developed content for an electronic survey of Canadian physicians’ practices regarding BoNT-A use for

childhood hypertonia, and subsequently interpreted the results of survey to understand the state of current practices and identify opportunities for future knowledge translation efforts when current practice deviated from international best practice.

Study Design and Participant Selection

This is a cross-sectional survey of Canadian physicians who currently administer BoNT-A to children with hypertonia. Ethics approval was obtained from Holland Bloorview Kids Rehabilitation Hospital Research Ethics Board. The goal was to identify and survey all Canadian physicians known to be using BoNT-A for children with hypertonia. Physicians were recruited using a partial snowball approach whereby members of the Canadian Physician Panel identified eligible local physicians in their respective regions of practice.

Data Collection

Using the international consensus statements as a foundation, the panel developed an electronic survey with a series of questions pertaining to physician demographics, hypertonia assessment, indications for BoNT-A use, BoNT-A safety, injection protocols including dosage and pain management, muscle localization techniques and adjunctive interventions. Fifty Canadian physicians were emailed this one-time anonymous survey, which remained online from April-June 2011.

Data Analysis

Aggregate data were analyzed using descriptive statistics and plots of frequencies, means, and standard deviations.

The indications were reported across the International Classification of Functioning, Disability and Health (ICF) domains of body function and structure and activity and participation⁷.

RESULTS

Respondent Demographics

Seventy-eight percent (39/50) of physicians who received the survey responded from British Columbia (6), Alberta (7), Saskatchewan (3), Manitoba (1), Ontario (16), Quebec (2), Nova Scotia (2) and New Brunswick (2). The majority of respondents indicated they practice in a rehabilitation/children’s treatment center. Subspecialty areas included physiatry, developmental paediatrics, orthopedics, and paediatric neurology. All treat children/youth aged between 1 to 19 years.

Assessment

Current use of assessment tools for paediatric hypertonia is summarized in Table 1.

Indications

The results of typical muscles injected (top three muscles per indication) for eight upper limb indications appear in Table 2 and for 13 lower limb indications appear in Table 3. There was variability in current practices using BoNT-A in children with spastic CP and hip subluxation: 41% of respondents do not inject for this indication, while 32% inject only if the child is losing range of hip abduction. A minority (21%) indicated they inject hypertonic muscles in the hip area regularly until there is clear progression of hip subluxation.

Safety

The perceived frequency of adverse events (AEs) is presented in Table 4 and the perceived severity of the AEs is summarized in Figure 1. Following injection, one child required

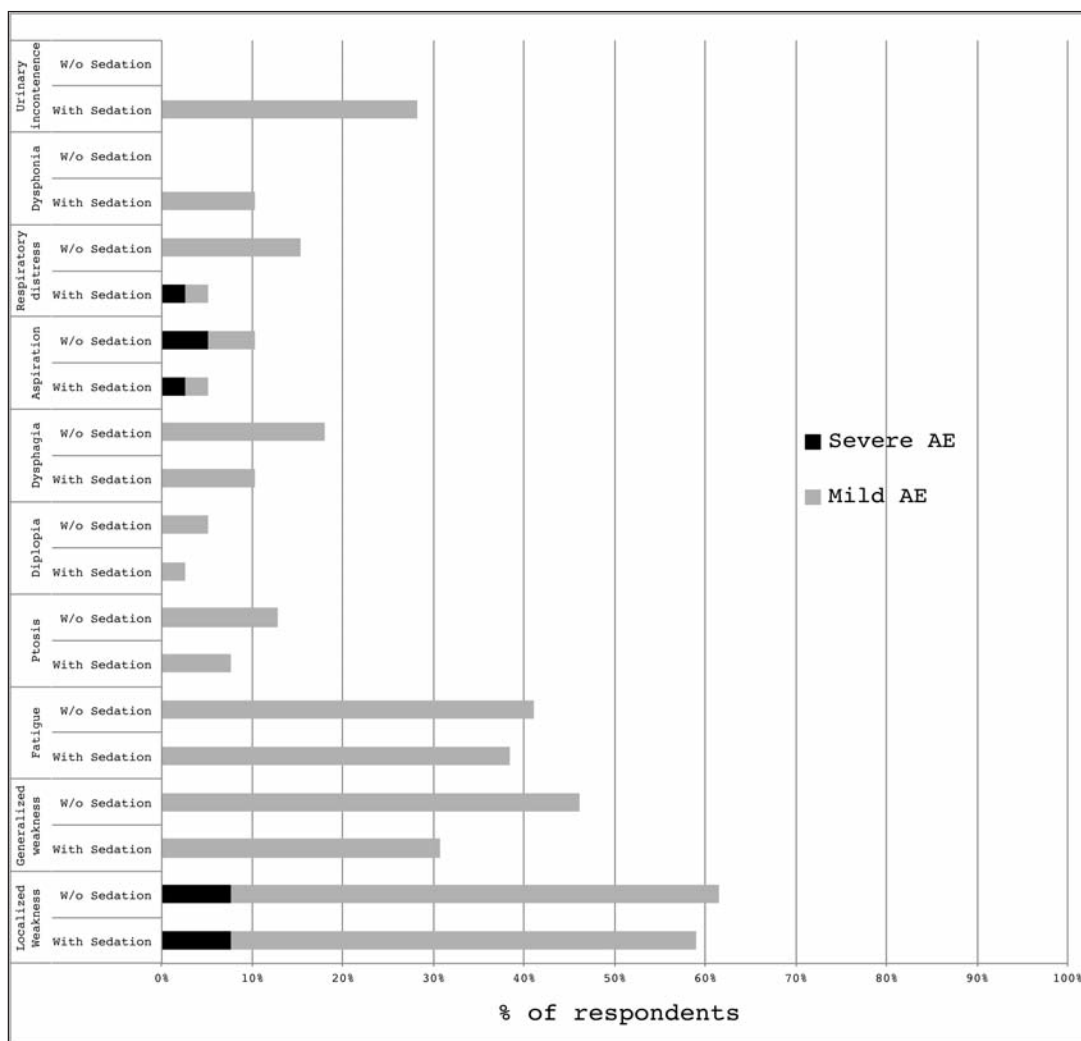


Figure 1: Perceived severity of adverse events post BoNT-A injections

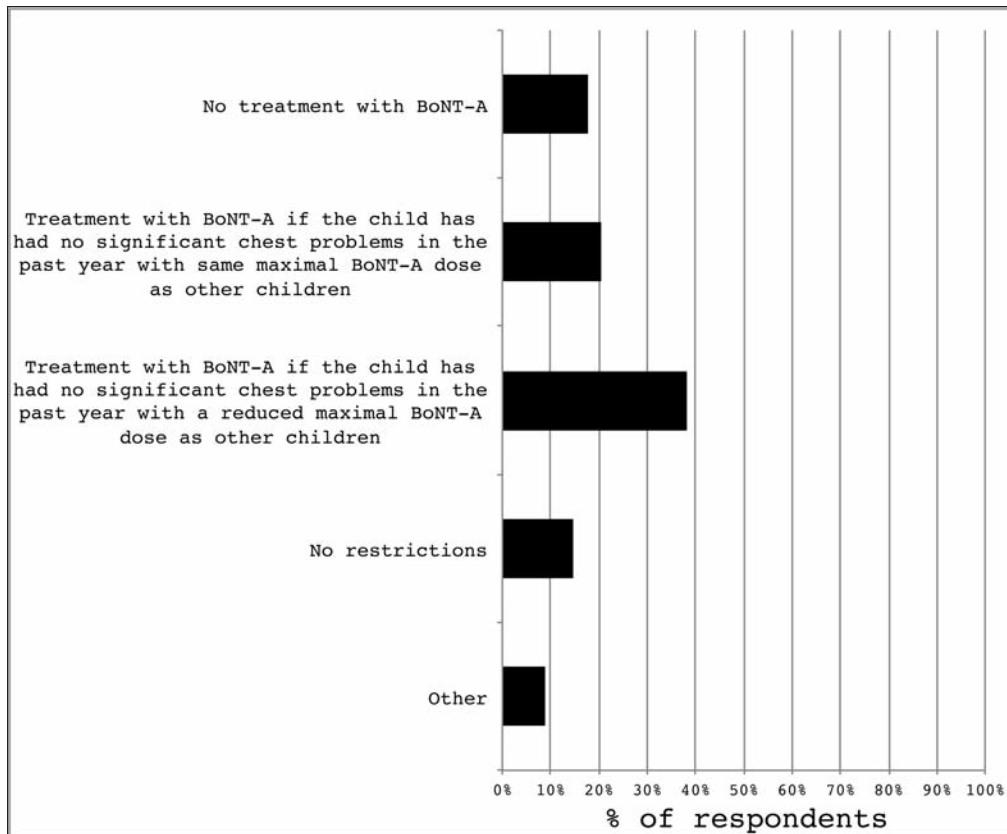


Figure 2: BoNT-A treatment options for children classified at GMFCS level V

hospitalization for aspiration. Three deaths were reported; one due to aspiration following surgery, and two that were interpreted to be associated with co-morbid medical conditions, not BoNT-A.

Seventy-five percent of physicians indicated they routinely obtain written informed consent about the potential risks of BoNT-A. When asked about AE monitoring, 59% reported that families self-report concerns, while 18% indicated that their clinics have implemented post-injection AE monitoring programs. Ninety-four percent of clinics give verbal information on adverse events, while 71% also distribute written information at the time of injection.

Injection Protocol

All respondents reported using onabotulinumtoxin A (Botox®) and 6% (n=2) reported experience with incobotulinumtoxin A (Xeomin®). Due to infrequent use of incobotulinumtoxin A, the remainder of the injection protocol refers to onabotulinumtoxin A (Botox®).

Fifty-two percent of physicians identified 16 Units/kg body weight of Botox® as the maximum amount injected. Thirty percent reported their maximum range between 6 to 12 Units/kg body weight, while 18% injected a maximum dosage of 20 Units/kg body weight. A majority (64%) reported a maximum 400 Units for injection at any one time; however 9% of physicians went over 800 Units. Dose per muscle calculations

were based on both body weight and total dose per muscle considerations for 85% of physicians.

Regarding dilution with normal saline, 79% reported using 2 ml (50 Units/ml) for lower limb injections. However, dilution for upper limb injections was more variable with 49% using 1 ml (100 Units/ml), and 36% using 2 ml (50 Units/ml).

Although three to five months was typically considered an appropriate re-injection interval by 74% of respondents, 30% favoured waiting six months or longer. Over 80% considered return of hypertonia or a clear treatment goal in determining re-injection timelines.

Management strategies vary for children with dystonia versus spasticity. Fifty-nine percent considered injecting agonist/antagonist muscle pairs in children with dystonia. There was no clear consensus on the use of BoNT-A in children/youth who are Gross Motor Function Classification System (GMFCS) Level V as indicated in Figure 2.

Localization Technique

All participants indicated routine use of palpation/anatomic knowledge, whereas electromyography (EMG), electrical stimulation (e-stim), and ultrasound are routinely used by 49%, 38%, and 19% of respondents respectively. For upper limb muscle localization, palpation/anatomic knowledge is the most frequently used localization technique except in the flexor digitorum profundus/superficialis and flexor pollicis longus

muscles where e-stim is more frequently used. For lower limb muscle localization, palpation/anatomic knowledge is also used routinely except for the tibialis posterior, flexor digitorum longus, and flexor hallucis longus where e-stim is more frequently used.

Pain Management During Injections

Distraction is the most frequently used pain management technique, used by 64% of responders, followed by EMLA (lidocaine cream) or general anesthetic with 21% of respondents. Use of sedation, music therapists, or childlife workers is relatively rare.

Adjunctive Interventions

The most commonly used adjunctive interventions are summarized in Table 2 and 3.

Follow-up Care

Seventy percent of participants see patients for short-term assessment following BoNT-A injections, scheduled anywhere from two weeks to three months post injection. Respondents indicated that the post-injection follow-up assessment was conducted by the clinic physician (68%), clinic occupational

therapist (55%), clinic physiotherapist (84%) or clinic nurse (23%). The majority (82%) of respondents indicated they could transition teens to an adult BoNT-A clinic once they reached 19 years.

DISCUSSION

The 50 physicians identified to receive the survey are likely to represent nearly all Canadian physicians known to be using BoNT-A for children with hypertononia. The 78% survey response rate is therefore adequate to provide generalizable results that reflect current Canadian practices.

Assessment

Canadian clinicians are following international consensus “expert opinion” recommendations in their routine use of the Modified Tardieu Scale to assess hypertononia severity and passive range of motion and the GMFCS to establish overall gross motor function. The Manual Ability Classification System (MACS), assessing bimanual ability to handle objects, was not frequently used. Formal measures assessing the impact of hypertononia on upper and lower extremity function are not routinely used, perhaps reflecting the time required for these assessments and the need for additional team members (e.g. therapist) to complete

Table 2: Muscles most frequently injected (top 3) and adjunctive interventions (top 2) for upper limb (UL) indications

INDICATION	Top 3 UL muscles injected	Adjunctive Interventions (Top 2 identified for each intervention)
Body Structure / Function		
Relieve muscle spasms	Trapezius (67%) Triceps brachii (58%) Extensor digitorum communis (56%)	Stretching (83%) Thermoplastic splinting (57%)
Pain management	Pectoralis major (44%) Trapezius (44%) Triceps brachii (42%)	Stretching (67%) Thermoplastic splinting (48%)
Improve thumb position	Flexor pollicis longus (100%) Flexor pollicis brevis/Opponens pollicis (100%) Adductor pollicis (94%)	Other splints (70%) Thermoplastic splinting (48%)
Elbow flexion	Brachioradialis (97%) Brachialis (93%) Biceps brachii (91%)	Stretching (80%) Thermoplastic splinting (70%)
Wrist flexion	Flexor carpi radialis (100%) Flexor carpi ulnaris (97%) Flexor digitorum profundus (64%) Flexor digitorum superficialis (64%)	Thermoplastic splinting (87%) Stretching (77%)
Activity / Participation		
Reduce tone to facilitate ease of dressing	Pectoralis major (100%) Brachioradialis (83%) Teres major (79%) Biceps brachii (79%)	Stretching (83%) Other splints (60%)
Improve cosmetic appearance of the hand/arm	Extensor digitorum communis (75%) Flexor carpi radialis (71%) Flexor carpi ulnaris (68%)	Thermoplastic splinting (54%) Stretching (50%)
Improve the use of hand in daily activities	Pronator quadratus (100%) Adductor pollicis (97%) Pronator teres (97%)	Stretching (71%) Thermoplastic splinting (71%)

Table 3: Muscles most frequently injected (top 3) and adjunctive interventions (top 2) for lower limb (LL) indications

INDICATION	Top 3 LL muscles injected	Adjunctive Interventions (Top 2 identified for each intervention)
Body Structure / Function		
Minimize loss of muscle length	Medial hamstrings (semimembranosus) (72%) Medial hamstrings (semitendinosus) (71%) Gastrocnemius (71%)	Stretching (90%) Thermoplastic splinting (77%)
Relieve muscle spasms	Adductor longus (61%) Adductor magnus (52%) Rectus femoris (50%)	Stretching (83%) Thermoplastic splinting (37%)
Pain management	Iliopsoas (60%) Adductor longus (58%) Adductor magnus (57%)	Stretching (79%) Thermoplastic splinting (37%)
Hip subluxation	Adductor longus (67%) Adductor magnus (56%) Gracilis (50%)	Stretching (63%) Other splints (74%)
Knee flexion	Medial hamstrings (semitendinosus) (94%) Medial hamstrings (semimembranosus) (94%) Lateral hamstrings (76%)	Stretching (90%) Other splints (74%)
Ankle plantar flexion	Gastrocnemius (97%) Soleus (94%) Peroneus longus/brevis (88%)	Stretching (94%) Other splints (74%)
Activity / Participation		
Reduce tone to facilitate ease of dressing	Adductor magnus (78%) Adductor longus (73%) Gracilis (63%)	Stretching (84%) Other splints (53%)
Reduce tone to facilitate hygiene	Adductor magnus (96%) Adductor longus (82%) Gracilis (67%)	Stretching (88%) Other splints (47%)
Improve/maintain 'gait' in child with unilateral spastic CP GMFCS I, II	Gastrocnemius (97%) Soleus (97%) Tibialis posterior (91%)	Thermoplastic splinting (94%) Stretching (91%)
Improve/maintain 'gait' in child with bilateral spastic CP GMFCS I, II	Medial hamstrings (semitendinosus) (97%) Medial hamstrings (semimembranosus) (97%) Gastrocnemius (94%)	
Improve/maintain 'gait' in child with bilateral spastic CP GMFCS III	Peroneus longus/brevis (100%) Adductor magnus (95%) Medial Hamstrings (Semimembranosus) (94%) Gastrocnemius (94%)	Stretching (94%) Thermoplastic splinting (91%)
Improve/maintain ability to transfer in child with CP GMFCS IV	Medial hamstrings (semitendinosus) (87%) Medial hamstrings (semimembranosus) (84%) Adductor magnus (81%)	Stretching (84%) Thermoplastic splinting (84%)
Improve/maintain ability to use a stander or walker for child with CP GMFCS IV	Gastrocnemius (91%) Medial hamstrings (semitendinosus) (87%) Medial hamstrings (semimembranosus) (87%) Iliopsoas (86%)	Thermoplastic splinting (87%) Stretching (80%)

Table 4: Physician identified perceived frequency of adverse events following BoNT-A injections with and without sedation

	Never	Rarely <1%	Occasionally 1-9%	Frequently >10%
Localized weakness	7%	23-24%	54-55%	14-15%
Generalized weakness	43-48%	52-57%	0-7%	0%
Fatigue	40-41%	47-52%	7-13%	0%
Ptosis	85-89%	11-15%	0%	0%
Diplopia	96-97%	3-4%	0%	0%
Dysphagia	78-80%	17-22%	0-3%	0%
Aspiration	89-93%	3-11%	0-3%	0%
Respiratory distress	86-97%	3-14%	0%	0%
Dysphonia	85-90%	10-15%	0%	0%
Urinary incontinence	58-63%	33-39%	3-4%	0%

% in cells refers to % of physicians responding in each category

them. Less than one third are routinely using tools to establish goals for BoNT-A intervention. Contrary to the consensus guidelines, half of the respondents are not routinely using a standard observation of gait in ambulatory children. Recommendations from the panel include routine use of the MACS to classify upper extremity function in children receiving BoNT-A, use of tools such as the Canadian Occupational Performance Measure (COPM) or the Goal Attainment Scale (GAS) to align the expectations of the physician, therapist and child/youth and family in response to treatment, as well as to measure change post BoNT-A treatment, and use of a standardized gait assessment tool for ambulatory children (GMFCS I – III).

Indications

The collection of data that pairs indications for BoNT-A with muscles commonly injected is unique to this survey and creates a useful reference for physicians planning injections. Indications for BoNT-A spanned the ICF framework focused on body structure, function and activity⁷. No specific indications at the ICF participation level or quality of life were identified in this survey, although goals such as facilitating ease of dressing and relief of pain can be seen as ways to optimize well being of the child, and to facilitate caregiving. To standardize indications for BoNT-A injections in Canada, the panel recommends development of a common language and coding system based on a core set of ICF items on body function, body structure and activities/participation level.

Safety

The survey results confirm numerous previous studies and consensus that injection of BoNT-A in children with cerebral palsy is generally safe⁸⁻¹⁵. Transient mild systemic adverse events, including generalized weakness, fatigue, ptosis, diplopia, dysphagia, aspiration, respiratory distress, dysphonia and temporary urinary incontinence may occur rarely in children after injection, especially in children with more physical limitations (GMFCS IV-V)⁸⁻¹³. In our survey, localized weakness close to the injection site, was the most frequently identified adverse event, estimated to occur occasionally (1-9%). Most adverse events in our survey were identified as mild; however localized weakness and aspiration/respiratory distress were classified as severe less than 10% of the time. The panel is in agreement with O'Flaherty et al. that there is insufficient evidence to warrant restriction of the administration of BoNT-A in children with cerebral palsy at any GMFCS level, based solely on concerns regarding adverse events^{14,15}. As recommended by Naidu et al., upper dose limits should be reviewed for children at all GMFCS levels, particularly those at levels IV and V with a history of aspiration and respiratory disease¹². In these children, alternatives to general anaesthesia may be particularly important. The long-term consequence of repeated BoNT-A injections on muscle morphology in growing children with cerebral palsy is unknown and was not addressed in this study¹⁶⁻¹⁹. The panel recommends routinely providing standardized verbal and written parental information about possible adverse events of BoNT-A prior to obtaining informed written consent for all injections. An adverse event monitoring program should be implemented. Botulinum toxin-A should be part of the medication

reconciliation process of children with CP²⁰. The National Health Protections Branch adverse events reporting should be utilized by physicians for serious or unexpected adverse events related to BoNT-A injections. Long-term effects of repeated use of BoNT-A on muscle in children requires further study.

Injection Protocol

In paediatric patients, the majority of physicians restricted the maximal dosage to 16 Units/kg body weight or 400 Units total dosage during a single treatment session. With new concerns about rare but clinically significant distant spread (e.g. generalized weakness), there have been questions about injecting children who have a more severe physical disability (GMFCS V). The lack of consistency in the survey responses reflect this uncertainty, however the most frequent pattern identified was continued usage of BoNT-A in children with GMFCS V at a reduced maximal dosage as long they did not have a history of chest problems in the preceding 12 months.

Localization Techniques

The international consensus statements⁴⁻⁶ recommend the use of injection techniques that allow the proper identification of the target muscle. This recommendation was based on “expert opinion”. Although evidence suggests that e-stim and ultrasound are superior to muscle palpation in the accuracy of needle placement in target muscles, there is insufficient evidence that either method results in superior clinical efficacy^{21,22}. It is not surprising that respondents reported ultrasound as the least frequently used method of localization as it was only recently introduced in Canada for this application.

Pain Management

The wide variation of pain management techniques is most likely explained by resource access disparities between different clinics. While distraction techniques can be incorporated in any clinic setting, specialized support such as child life workers/trained nurses or the use of sedation and the support of anesthesiologists may only be available in tertiary centers. The variation in practice patterns suggests this may be an area that requires further study and advocacy around resources.

Adjunctive Interventions and Follow-Up Care

Following BoNT-A injections in the upper extremity, stretching and use of splints were the most common adjunctive treatments utilized. In the lower extremity, strengthening and serial casting were also frequently endorsed. Variability in practice was identified. This is understandable given the lack of evidence regarding the efficacy and optimum delivery of these interventions. In the absence of evidence-informed treatment protocols, the panel suggests that practitioners monitor and measure each patient's response in order to individualize adjunctive interventions following BoNT-A injections.

Follow-Up Care

The panel recognizes that workload may preclude routine early review by many injecting practitioners. However, early physician review should occur in the setting of adverse events and treatment failures.

Most paediatric injectors identified that they are able to refer to an adult clinic, but the panel raises the concern that a significant number, 21%, cannot. Transition from paediatric to adult health care providers, including hypertonicity management, should be included in regional health care service planning.

CONCLUSION

Overall, Canadian physicians are adhering to current international best practices when using BoNT-A to treat paediatric hypertonia. Opportunities for enhanced practice when compared with the international consensus guidelines were identified in the following areas: the use of individualized goal setting prior to initiating BoNT-A, and enhanced usage of localization techniques. It is interesting to note that both of these international recommendations are based on expert opinion rather than being informed by evidence. This survey provides a useful frame of reference for current dosing practice, muscles commonly injected for different indications, and perceived frequency of adverse events. Areas of advocacy for enhanced resources or services were identified for procedural pain management and adult hypertonia clinics. Further research is recommended in the use of localization techniques for injection, the use of standardized goal setting prior to BoNT-A injections, evaluation of the long-term impact of BoNT-A on muscle morphology, the use of BoNT-A for hip subluxation, and the impact on activity, participation and quality of life.

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