Ботулинотерапия. Новые публикации 2018 года, важные для клинициста

Проф. Ахмадеева Лейла Ринатовна, Башкирский медуниверситет

Экспертный Совет, г. Уфа, 15 декабря 2018г

Цель:

Обсудить ряд статей из зарубежных рецензируемых журналов, опубликованных в текущем году и *отсутствующих в бесплатном доступе*, важных для клинициста-невролога, работающего с взрослыми пациентами с использованием препаратов ботулинического нейропротеина типа А

Тематика:

1. Обзорно-аналитические статьи
2. Новые данные по патофизиологии и анатомии
3. Техники, применяемые при выполнении инъекций

ОБЗОРЫ

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Recent developments in clinical trials of botulinum neurotoxins

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Marketed BoNT products.

Brand name	FDA generic name	Manufacturer	Country
Botox, Vistabel, Vistabex, Botox Cosmetic	onabotolinumtoxinA	Allergan	USA
Dysport, Reloxin, Dysport Cosmetic	abobotulinumtoxinA	Ipsen	UK France
Xeomin	incobotulinumtoxinA	Merz	Germany
Myobloc, Neurobloc	rimabotulinumtoxinB	Solstice	USA
Neuronox, Botulif, Cunox, KbtxA, Meditoxin, Neuramis, Siax, MT 10107, MT 10109, Meditoxin injection - Medy-Tox		Medytox	Korea
Prosigne, BTX-A, CBTX-A, Hengli, Lantox		Lanzhou Biological Products	China
Botulax		Hugel	Korea
PurTox		Mentor Corporation	USA
Nabota, DWP-450, Evosyal		Daewoong Pharmaceutical	Korea

Unpublished and ongoing clinical trials on topical botulinum toxin (source: Clinicaltrails.gov).

Study	Compound, Producer	Trial Design *	Indication	Duration	Outcome measures	Results/status
NCT01776606	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Lateral canthal lines	Week 4 Week 4	Primary: Composite endpoint based upon the IGA and patient assessment of severity of lateral canthal lines. Secondary: Proportion of subjects with 2 point or greater improvement from baseline using the IGA; Proportion of subjects with 1 point or greater improvement from baseline using the IGA; Proportion of subjects with a 2 point or greater improvement from baseline using the SSA	Completed; no study results posted
NCT01940991	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Severe Crow's Feet Lines	=	=	Completed; no study results posted
NCT01064518	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Lateral Canthal Lines	Week 4 Week 8	Primary: improvement based on the investigator global and patient assessments. Secondary: improvement based on the investigator global and patient assessments.	Completed; no study results posted
NCT01124552	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Moderate to Severe Lateral Canthal Lines	Week 4 Week 4	Primary: Subject improvement based on the IGA Secondary: Subject Improvement and number of subjects based on investigator and patient assessments.	Completed; no study results posted
NCT00968825	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Moderate to Severe Lateral Canthal Lines	Week 4 Week 4 and 6	Primary: The number of subjects classified as exhibiting improvement via the IGA of Lateral Canthal Line Severity at Rest; incidence of treatment emergent AEs Secondary Outcome Measures: The number of subjects classified as exhibiting improvement via the IGA of Lateral Canthal Line Severity at Rest and Smile; incidence of treatment emergent AEs	Completed; no study results posted
NCT00968942	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Moderate to Severe Lateral Canthal Lines	Week 8 Weeks 2, 4, 6, 8	Primary: The number of subjects classified as exhibiting improvement via the IGA of Lateral Canthal Line-Rest Severity Scale of the LCA; incidence of treatment emergent AEs Secondary: The number of subjects classified as exhibiting improvement via the Investigator Global Assessment of Lateral Canthal Line Severity at Smile and at Rest; incidence of treatment emergent AEs	Completed; no study results posted
NCT00888914	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Moderate to Severe Lateral Canthal Lines	Day 28 Day 28	Primary: The number of subjects classified as exhibiting improvement via the Investigator Global Assessment at Smile Secondary: The number of subjects classified as exhibiting improvement via the Investigator Global Assessment at Rest; Incidence of treatment-emergent AEs	Completed; no study results posted
NCT00907387	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Moderate to Severe Lateral Canthal Lines	Day 28 Day 28	Primary: The number of subjects classified as exhibiting improvement via the IGA at Rest Secondary: Incidence of treatment-emergent adverse events	Completed; no study results posted
NCT00884234	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Moderate to Severe Lateral Canthal Lines	Week 6	Primary Outcome Measures: The number of subjects classified as exhibiting improvement via the Investigator Global Assessment from Baseline to End of Study; Incidence of treatment emergent AEs.	Completed; no study results posted
NCT02580370	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Lateral Canthal Lines	Week 4 Week 4	Primary: Composite endpoint based upon IGA and PSA Secondary: IGA with 2 points or greater improvement from baseline; IGA with 1 point or greater improvement from baseline; patient Severity Assessment with 2 points or greater improvement from baseline; Proportion of subjects with a 1 point or greater improvement from baseline using the Patient Severity Assessment	Completed; no study results posted
NCT01358695	ANT-1207	Randomized, double-blind, placebo controlled	Lateral Canthal Lines		Primary: IGA Score. Wrinkle scale with definitions of severity Secondary: SSA scale; IGA scale	Completed; no study results posted
NCT01951742	ANT-1401	Randomized, double-blind, placebo controlled	Crow's Feet (Lateral Canthal Lines)		Primary: IGA scale. Crow's Feet Wrinkle Scale Secondary: SSA score. Subjects self assessment of severity of Crow's Feet	Completed; no study results posted
NCT01809964	ANT-1401	Randomized, double-blind, placebo controlled	Lateral Canthal Lines		Primary: IGA Scale [Time Frame: Week 4] Secondary: SSA [Time Frame: Week 4]	Completed; no study results posted
NCT01293552	ANT-1207	Randomized, double-blind, placebo controlled	Acne Vulgaris		Primary: Efficacy will be assessed by lesion count. [Time Frame: Week 4] Secondary: Change from Baseline in IGA Score [Time Frame: Week 1, 2, 4, 8, and 12]. Change from Baseline in Lesion Count [Time Frame: Week 1, 2, 4, 8, 12]	Completed; no study results posted
NCT02479139	ANT-1207	Randomized, double-blind, placebo controlled	Primary Axillary Hyperhidrosis		Primary: HDSS [Time Frame: 12 Weeks]; GSP [Time Frame: 12 Weeks] Secondary: HDSS [Time Frame: Week 4, 8, and 18]; GSP [Time Frame: Week 4, 8, and 18]	Completed; no study results posted
NCT01799824	ANT-1403	Randomized, double-blind, placebo controlled	Primary Axillary Hyperhidrosis		Primary: HDSS [Time Frame: Week 8] Secondary: GSP [Time Frame: Week 8]	Completed; no study results posted

Abbreviations*, AAN Class of evidence ...; HDSS, Hyperhidrosis Disease Severity Scale; GSP, Gravimetric Sweat Production; SSA, Subject Self Assessment; IGA, Investigator Global, PSA, patient assessment of severity Assessment scale. Inflammatory lesion count (papules, pustules, and nodules) and non-inflammatory lesion count (open and closed comedones).

Unpublished and ongoing clinical trials on botulinum toxin injections in epicardial fat pads for preventing recurrences of atrial tachyarrhythmia (source: Clinicaltrails.gov).

Study	Compound	N° of patients	Trial Design	Procedure	Follow up	Outcome Measures	Results/status
NCT02982434	Pharmaceutical composition containing botulinum toxin	180	Randomized, double-blind, placebo controlled	CABG	12 months	Primary: Freedom from any atrial tachyarrhythmias; Recurrence of >30 s of any atrial tachyarrhythmia, including atrial fibrillation and atrial flutter/tachycardia, after cardiac surgery procedure with no antiarrhythmic drug. Secondary: number of deaths; time intervals from end of surgery to weaning from ventilation, extubation and discharge from ICU; incidence of congestive heart failure; incidence of sustained ventricular arrhythmias; stroke or transient ischemic attack; incidence of myocardial infarction; rehospitalization	Recruiting Estimated Study Completion Date: February 2018
NCT02498769	Botulinum Toxin Type A	130	Randomized, double-blind, placebo controlled	CABG, valve surgery or CABG + valve surgery with cardiopulmonary bypass	up to two weeks	Primary: Time to in-hospital POAF [determined by ECG or telemetry.] Secondary: Incidence of in-hospital POAF; Length of stay; Adverse events.	Recruiting Estimated Study Completion Date: July 2018
NCT02617069	Botulinum toxin injection	170	Randomized, double-blind, placebo controlled	cardiac surgery	1 month 12 months	Primary: Recurrence of >30 s of any atrial tachyarrhythmia, including AF and atrial flutter/tachycardia, after cardiac surgery procedure with no antiarrhythmic drug. Secondary: Recurrence of >30 s of any atrial tachyarrhythmia, including AF and atrial flutter/ tachycardia, after cardiac surgery procedure with no antiarrhythmic drug.	Recruiting Estimated Study Completion Date: March 2017

Abbreviations: CABG, coronary artery bypass graft; POAF, postoperative atrial fibrillation; AF, atrial fibrillation.

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Evidence on botulinum toxin in selected disorders

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Botulinum toxin treatment of pain syndromes –an evidence based review

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This PowerPoint Template has clean and neutral design that can be adapted to any content and meets various market segments. With this many slides you are able to make a complete PowerPoint Presentation that best suit your needs.

Pain syndromes with level A evidence of efficacy (effective) based on two or more Class I, randomized double blind, placebo controlled clinical trials.

Authors	Pain Syndrome	AAN Class	Study design	Number of patients	Type of toxin/dose	Results
Xiao et al., 2010	Post-herpetic neuralgia	I	Parallel	60	Proscine * BoNT-A 100 units	Pain (VAS), sleep improved (S)
Apalla et al., 2013	Post- herpetic neuralgia	I	Parallel	30	onaBoNT-A 100 units	Pain(VAS), quality of sleep improved (S)
Ranoux et al., 2008	Post-traumatic neuralgia	I	Parallel	24	onaBoNT-A 20–190 units	Pain (VAS), brush sensitivity improved (S)
Attal et al., 2016	Post-traumatic neuralgia	I	Parallel	46	onaBoNT-A 20–190	Pain (VAS) and sleep improved (S)
Wu et al., 2012	Trigeminal neuralgia	I	Parallel	40	Proscine BoNT-A 75 units	Pain (VAS), PGIC Improved (S)
Zhang et al., 2014	Trigeminal neuralgia	I	Parallel	84	Proscine BoNT-A 25 & 75 units	Pain (VAS), PGIC Improved (S) No difference between low and high dose

Proscine: Chinese type A toxin from Lanshou Institute; (S) significant $P < 0.05$) PGIC: Patient's global expression of change.

Pain syndromes with level B evidence of efficacy (probably effective) based on one Class I or two Class II, randomized double blind, placebo controlled clinical trials.

Authors	Pain Syndrome	AAN Class	Study design Site of injection	Number of patients	Type of toxin/dose	Results
Yuan et al., 2009	Diabetic neuropathy	II	Crossover intradermal	18	onaBoNT-A/50	VAS, Sleep quality index improved (S)
Ghasemi et al., 2014	Diabetic neuropathy	I	Parallel Intradermal	40	aboBoNT-A 100 units	VAS and NPS improved (S)
Babcock et al., 2005	Plantar Faciitis	II	Parallel Medial heel, mid-foot	27	onaBoNT-A 70 units	VAS, Maryland foot score (MFS), pressure algometry improved (S)
Huang et al., 2010	Plantar Faciitis	II	Parallel below calcaneus into plantar fascia (ultrasound)	50	onaBoNT-A 50 units	VAS improved −plantar fascia thickness reduced (S)
Peterlein et al., 2012	Plantar Fasciitis	II	Parallel Fan shape manner, origin of plantar fascia	40	aboBoNT-A 200 units	VAS: proportion of responders: AboBoNT-A 25%, placebo 5% (nS)
Elizondo-Rodriguez et al., 2013	Plantar Faciitis	II	Comparator dexamethasone	40	aboBoNT-A 250 units	More improvement of VAS, MFS, FADI in the toxin group (S)
Fishman et al., 2002	Piriformis syndrome	II	Parallel Into piriformis	70	onaBoNT-A 200 units	Pain (VAS) improved in toxin group (S)
Childers et al., 2002	Piriformis syndrome	II	Crossover Piriformis muscle	9	onaBonT-A 100 units	Improvement of pain (VAS) (S)
Fishman et al., 2016	Piriformis Syndrome	II	Parallel Piriformis muscle	56	incoBoNT-A 300 units	Pain(VAS) and FAIR physical score improved in toxin group (S)
Foster et al., 2001	Low back pain	II	Parallel Extensor spinae	31	onaBoNT-A 200 Units (unilateral)	Pain(VAS), Oswestry score improved in the toxin group (S)
Machado et al., 2016	Low back pain	II	Parallel Extensor spine	37	IncoBoNTA	Pain (VAS), PIGI, Oswestry scores (all S)
Wong et al., 2005	Lateral epicondylitis	I	Parallel	60	aboBoNT-A/60 units	Pain (VAS) improved (S)
Hayton et al., 2005	Lateral epicondylitis	II	Parallel	40	aboBoNT-A/50 units	Pain(VAS), SF12 (nS)
Placzek et al., 2007	Lateral epicondylitis	I	Parallel	130	aboBoNT-A/60 units	Pain (VAS), patient satisfaction (S)
Espandar et al., 2010	Lateral epicondylitis	II	Parallel	48	aboBoNT-A/60 units	Pain(VAS) Pain(maximum pinch) (S)
Gottsch et al., 2011	Male Pelvic Pain-prostatitis	II	Parallel bulbospongiosus	13	onaBoNT-A/ 100 units	Pain(VAS), CPSI
Falahatkar et al., 2015	Male pelvic pain -Prostatitis	I	Parallel Lateral lobe of prostate, 3 points	60	aboBoNT-A/100 & 200 units	Pain (VAS) NIH: CPSI NIH: QoL All (S)
Han et al., 2016	Neuropathic pain after spinal cord trauma	I	Parallel subcutaneous	40	BonT-A (korean) 200 units	Pain(VAS) improved(S) WHO -QoL test showed a trend improvement ($p = 0.052$)
Breuer et al., 2006	Carpal Tunnel Syndrome	I	Parallel Divided into 3 hypothenar muscles	20	rimaBoNT-A 2500 units	Pain(VAS): No significant difference between BoNT and placebo

VAS: visual analog scale; (S) significant $p < 0.$; (nS) non-significant $P > 0.05$; QL: qadratus lumborum; MFS: Maryland foot score; FADI: Foot Ankle disability Index; CPSI: Chronic prostatic symptom index; OOL: quality of life.

Pain disorders with level C evidence of efficacy (possible effective) based on availability of one class II study (randomized, double blind, placebo controlled).

Authors	Pain disorder	AAN Class	Design Site of injection	Number of patients	Toxin and dose	Results
Abbott et al., 2006	Female Non-menstrual pelvic pain	II	Parallel Puborectalis pubococcygeus	60	OnaBoNT-A 80 units bilaterally	Alleviated Pain(VAS) (S) and dyspareunia (S)
Kuo et al., 2016	Painful bladder (interstitial cystitis)	II	Parallel, suburothelial	60	onaBoNT-A 100 units divided in 20 sits (5 units/site)	Pain (VAS) improved (S) Success rate 63% in BoNT and 15% in the saline group
Sing et al., 2010	Pain after total knee arthroplasty	II	Parallel Intra-articular	54	onaBoNT-A 100 units	Pain(VAS), MMOAI, PGIC all improved (S)
Sing et al., 2009	Shoulder Arthritic pain	II	Parallel Intra-articular	43	OnaBoNT-A 100 units	Pain(VAS) improvement (S), Disability Index: Trend ($p = 0.08$)
Singer et al., 2010	Knee pain -vastus lateralis imbalance	II	crossover Intra-articular	24	AboBoNT-A 500 units	Pain(VAS), walking, kneeling Improved (S)
Barwood et al., 2000	Pain after adductor release surgery (children)	II	Parallel Adductors Bilaterally	16	OnaBoNT-A 8 units/Kg	Pain(VAS) Improved (S)

VAS: visual analog scale MOAI: Mc Master osteoarthritis index.

Randomized, placebo-controlled (Class I&II) trials of botulinum neurotoxins in Myofascial Pain Syndrome.

Author	Class	No	Location	primary outcome (PO)	Drug & Dose	Results
Cheshire et al., 1994	II	6	cervical	VAS at wks 2,4,8	Ona-A, 15–25/tp	PO met $P < 0.05$
Wheeler et al., 1998	II	26	Cervical Thoracic	pressure algometer at wks 1,3,6,8,12	Ona-A: 50 and 100u/tp	PO not met
Freund and Schwartz 2000	II	26	Cervical	VAS, ROM, at 4Wks	Ona-A,20u/tp	PO met $P < 0.01$
Wheeler et al., 2001	II	50	cervical	NPAD,GAI, SF-36 Wks 4,8,12,16	Ona-A,231 ± 50	PO not met
Ferrante et al., 2005	II	142	cervical/Shoulder	VAS,PPT,SF-36 weeks 1,2,8,12	Ona-A, 10,25, and 50u/tp	PO not met
Göbel et al., 2006	I	144	upper back	Proportion of patients With mild or no pain At week 5	Abo-A,40u/tp Total:400U	PO: met $P = 0.002$
Oerama et al., 2006	II	30	infraspinatus	VAS: at wks 3 & 28	Ona-A 50u/tp Total 50 U	PO: not met
Lew et al., 2007	II	29	cervical/	VAS, NDI,SF-36 at 2 months	Ona-A 50u/tp Total: 200 U	PO: not met
Benecke et al., 2011	I	153	cervical/Shoulder	proportion of patients with mild or no pain At week 5	Abo-A 50u/tp Total: 400U	PO: not met
Kwanchuay et al., 2015	II	20	Shoulder Trapezius	VAS 3 & 6 weeks Single injection	onaA- 20 U	PO: not met

PO = primary outcome measure; VAS = pain intensity in visual analog scale; ROM = range of motion; ona-A = onabotulinum toxin A; aboA = abobotulinum toxinA, NPAD = neck pain and disability scale; GAI = global assessment of improvement; PPT = pain pressure threshold; VRS = verbal reporting score; tp = trigger point; NDI = neck disability index; PF = pain frequency; ns = not significant.

the efficacy of BoNTs in trigeminal, post-herpetic and post-traumatic neuralgias. There is further evidence from class I and II studies that BoNTs are probably effective in diabetic neuropathy, plantar fasciitis, piriformis syndrome, low back pain, male pelvic pain, lateral epicondylitis, and neuropathic pain after traumatic spinal cord injury. Other indications are forthcoming and require more refined investigations. Much remains to be learned about the optimal dose of botulinum toxins and optimal techniques of injection for different pain syndromes.

ПАТОГЕНЕЗ

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Direct central nervous system effects of botulinum neurotoxin

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Local intramuscular injections of botulinum neurotoxin type A (BoNT/A) are effective in the treatment of focal dystonias, muscle spasms, and spasticity. However, not all clinical effects of BoNT/A may be explained by its action at peripheral nerve terminals. For example, the therapeutic benefit may exceed the duration of the peripheral neuroparalysis induced by the neurotoxin. In cellular and animal models, evidence demonstrates retrograde transport of catalytically active BoNT/A in projection neurons. This process of long-range trafficking is followed by transcytosis and action at second-order synapses. In humans, several physiological changes have been described following intramuscular delivery of BoNT/A. In particular, clinical studies have documented a decrease in Renshaw cell-mediated inhibition (i.e., recurrent inhibition), which may be important therapeutically for normalizing uncoordinated movements and overflow of muscle activity. In this review, we present data obtained in animal and experimental models that support direct central actions of BoNT/A mediated via retrograde axonal trafficking. We also discuss the reorganization of central circuitry induced by BoNT/A in patients, and the potential contribution of these effects to the therapeutic efficacy of the neurotoxin.

Altogether, these data point to a significant role of CNS effects in the clinical benefits of BoNT/A. Importantly, not all the therapeutic activities of this neurotoxin can be explained solely on the basis of the blockade of neurotransmission at the neuromuscular junction. This prompts the need for a more detailed understanding of the mechanisms of BoNT/A central action and their contribution to the functional improvements.

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Botulinum toxin type A relieves sternocleidomastoid muscle fibrosis in congenital muscular torticollis

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Congenital muscular torticollis (CMT) is a neck deformity that involves shortening of sternocleidomastoid muscle (SCM) characterized by muscle atrophy and interstitial fibrosis. To investigate wheatear Botulinum toxin type A (BTA) has anti-fibrotic effects in CMT, we established acquired muscular torticollis that mimetics CMT in rabbit by intra-SCM injection of anhydrous alcohol. The treatment groups received BTA (2.5 units or 5 units) injection into the fibrotic SCM. The shortening and thickening of SCM were recorded by B-mode ultrasound. Changes in Col1A1, Fn, α-SMA expression were determined by immunohistochemistry. In vitro studies, TGF-β induced NIH3T3 fibroblasts were used to evaluate anti-fibrosis effect of BTA. Expression of the myofibroblast marker α-SMA and fibrosis markers Col1A1 and Fn were detected by Western blotting and quantitative RT-PCR. Our results showed that BTA injection attenuated shortening and thickening of fibrotic SCM. Elevated expression of Col1A1, Fn, α-SMA were confirmed in this fibrotic muscle model but reversed after BTA injection. Similar results observed in TGF-β induced NIH3T3 fibroblasts in both mRNA and protein levels. In conclusion, our results suggested that BTA could be a promising agent against SCM fibrosis in CMT through regulating fibroblast and inhibiting myofibroblast differentiation.

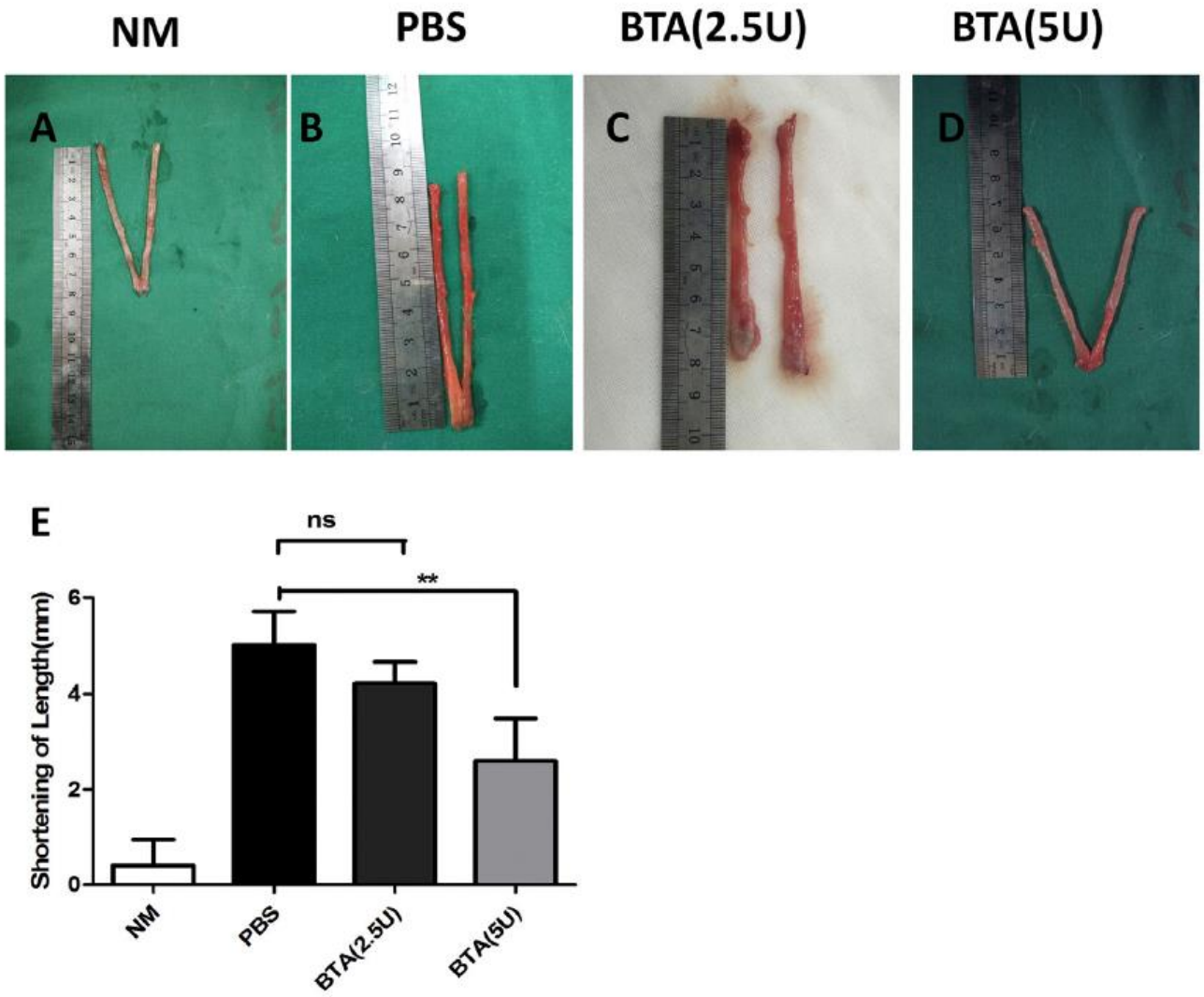


Fig. 1. BTA extended the length of the SCM of rabbit CMT model induced by anhydrous alcohol injection. (A) Normal rabbit SCM. SCM of CMT model rabbit treated with PBS (B), BTA 2.5 units(C), BTA 5 units (D). (E) The shortening of length analysis of the SCM between the normal rabbit and the rabbit CMT model with the treatment of control PBS, BTA 2.5 units and BTA 5 units, respectively. Data are presented as means ± SD; Error bars = SD; ns, not significant ($p = 0.6398$); $^{**}p = 0.0015$.

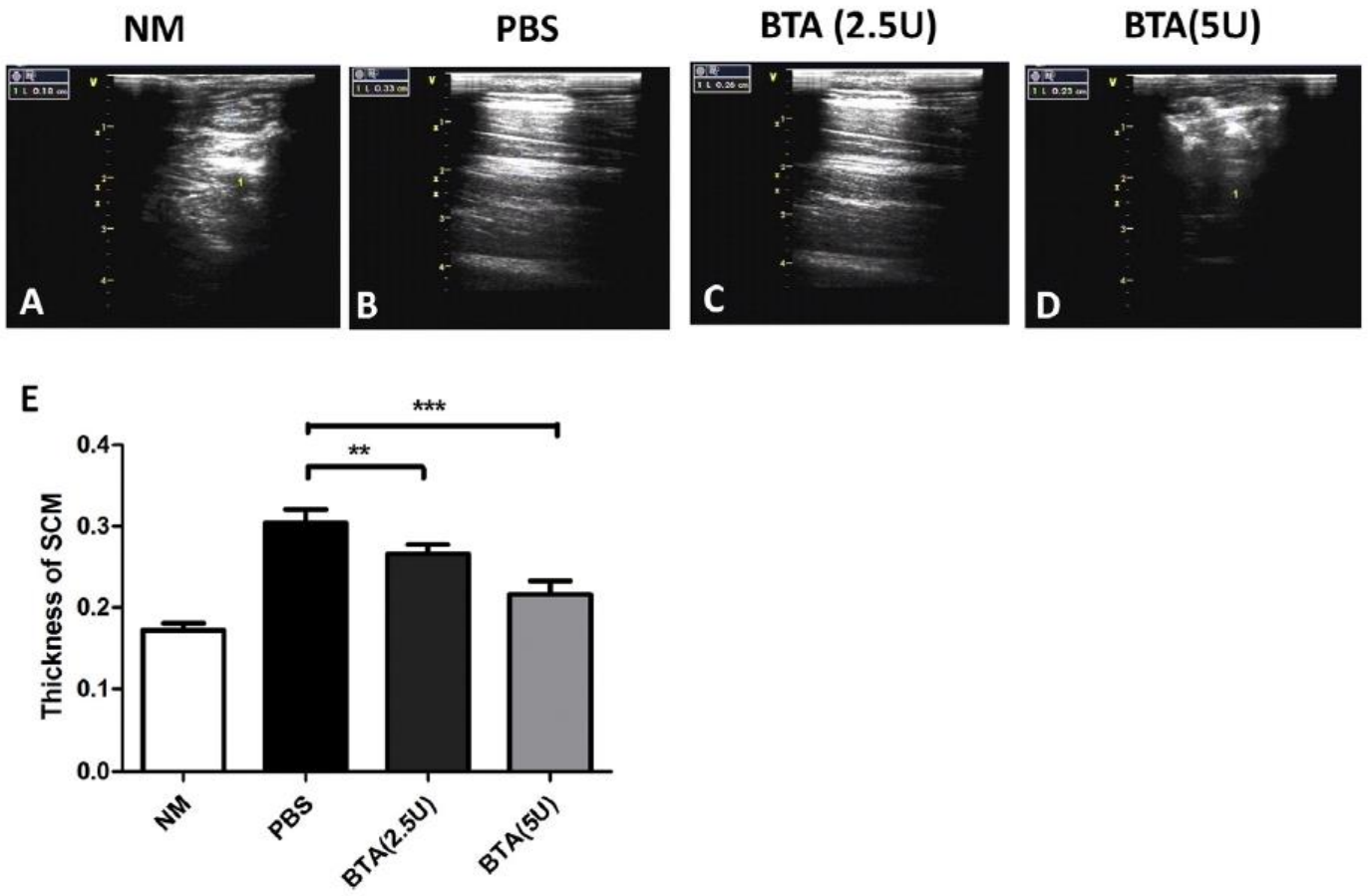


Fig. 2. BTA decreased the thickness of the SCM of rabbit CMT model induced by anhydrous alcohol injection. (A) Normal rabbit SCM. SCM of CMT model rabbit treated with PBS (B), BTA 2.5 units (C), BTA 5 units (D). (E) The thickness of the SCM between the normal rabbit and the rabbit CMT model with the treatment of control PBS, BTA 2.5 units and BTA 5 units, respectively. Data are presented as means ± SD; Error bars = SD; $^{**}p < 0.01$, $^{***}p < 0.0001$.

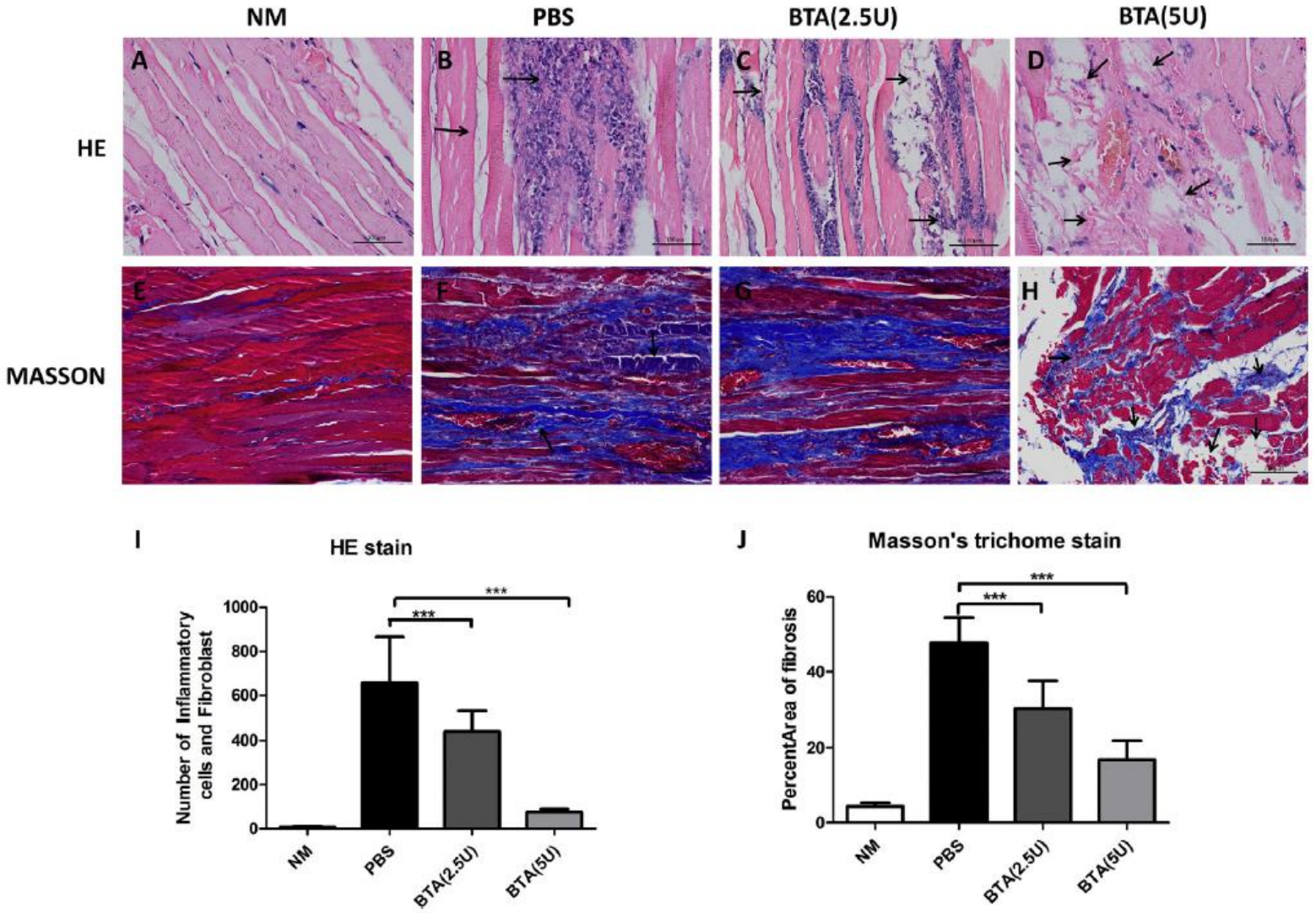


Fig. 3. BTA could degrade fibrotic SCM tissue of rabbit CMT model induced by anhydrous alcohol injection. (A, E) the normal rabbit SCM tissue characteristic with HE and Masson's trichrome staining. HE and Masson's trichrome stained SCM sections of rabbit CMT model treated with control PBS(B, F), BTA 2.5 units(C, G), BTA 5 units(D, H), respectively. The scale bar in A~H figures is 100 μm. (I) The number of inflammatory cells and fibroblast were counted to compared the fibrosis degree of SCM with different treatment. (J) The degree of SCM fibrosis with different treatment was analyzed by calculating the area of blue as a percentage of the total area. Data are presented as means ± SD; Error bars = SD; *** $p < 0.0001$.

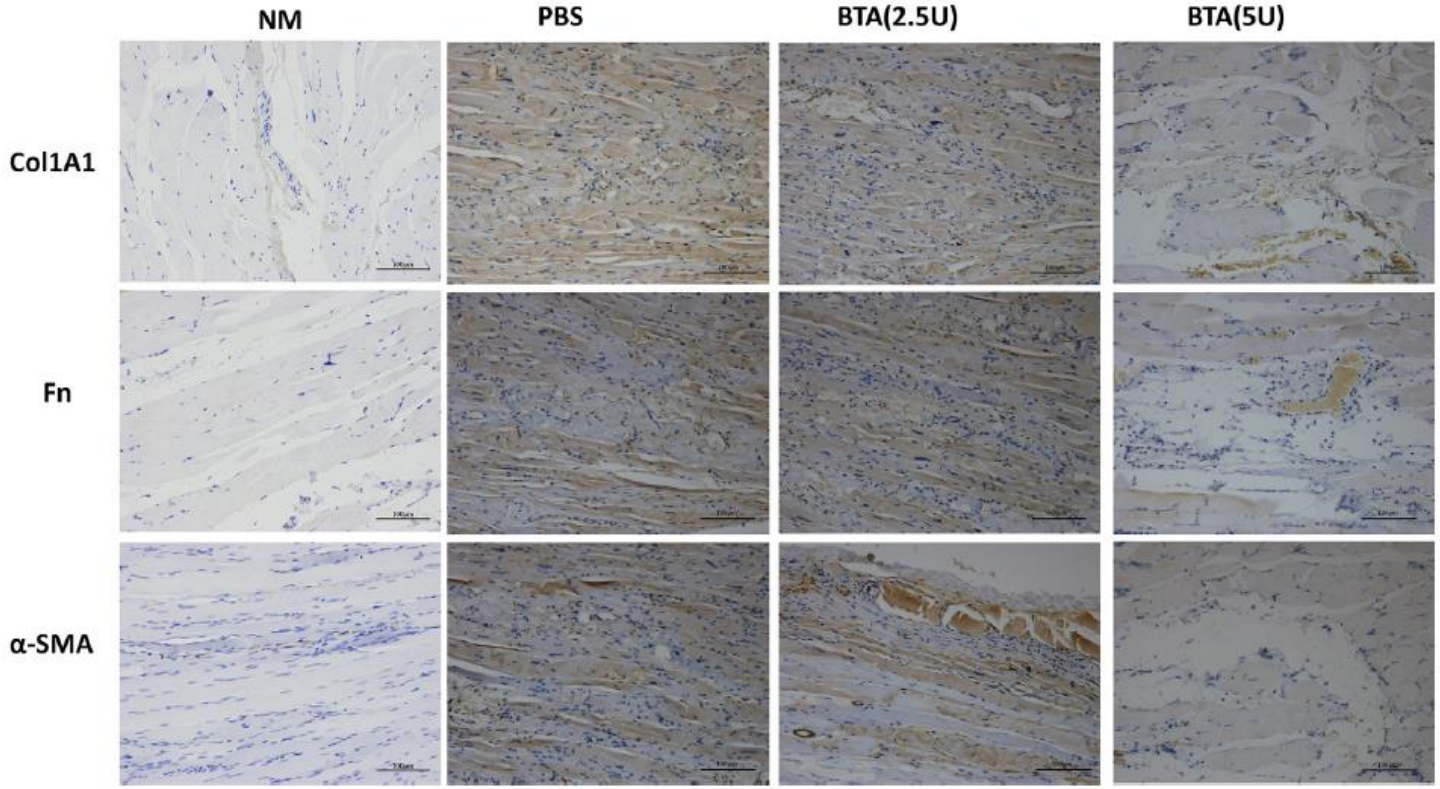


Fig. 4. BTA decreased the number of myofbroblast marker α-SMA and fibrosis markers Col1A1 and Fn. The immunohistochemistry evaluated expression of Col1A1, Fn and α-SMA in normal rabbit SCM, rabbit CMT model treated with control PBS, BTA 2.5 units, BTA 5 units respectively. The scale bar in figures is 100 μm.

Table 1
Immunohistochemical expression of Col1A1, Fn and α-SMA in SCM with different treatment.

Protein	NM n = 5 * 10	PBS n = 5 * 10	BTA(2.5 U) n = 5 * 10	BTA(5 U) n = 5 * 10	χ^2	*P* value
Col1A1 [n (%)]					152.062	<0.0001
Score 0	42(84%)	0(0%)	2(4%)	7(24%)		
Score 1	8(16%)	13(26%)	31(76%)	29(58%)		
Score 2	0(0%)	37(74%)	17(20%)	14(18%)		
Fn [n(%)]					136.364	<0.0001
Score 0	44(88%)	1(0%)	3(6%)	13(30%)		
Score 1	6(12%)	21(18%)	36(72%)	30(60%)		
Score 2	0(0%)	28(82%)	11(22%)	7(10%)		
α-SMA [n (%)]					76.496	<0.0001
Score 0	35(78%)	1(2%)	3(6%)	9(18%)		
Score 1	11(22%)	27(54%)	33(80%)	31(74%)		
Score 2	4(0%)	22(44%)	14(14%)	10(8%)		

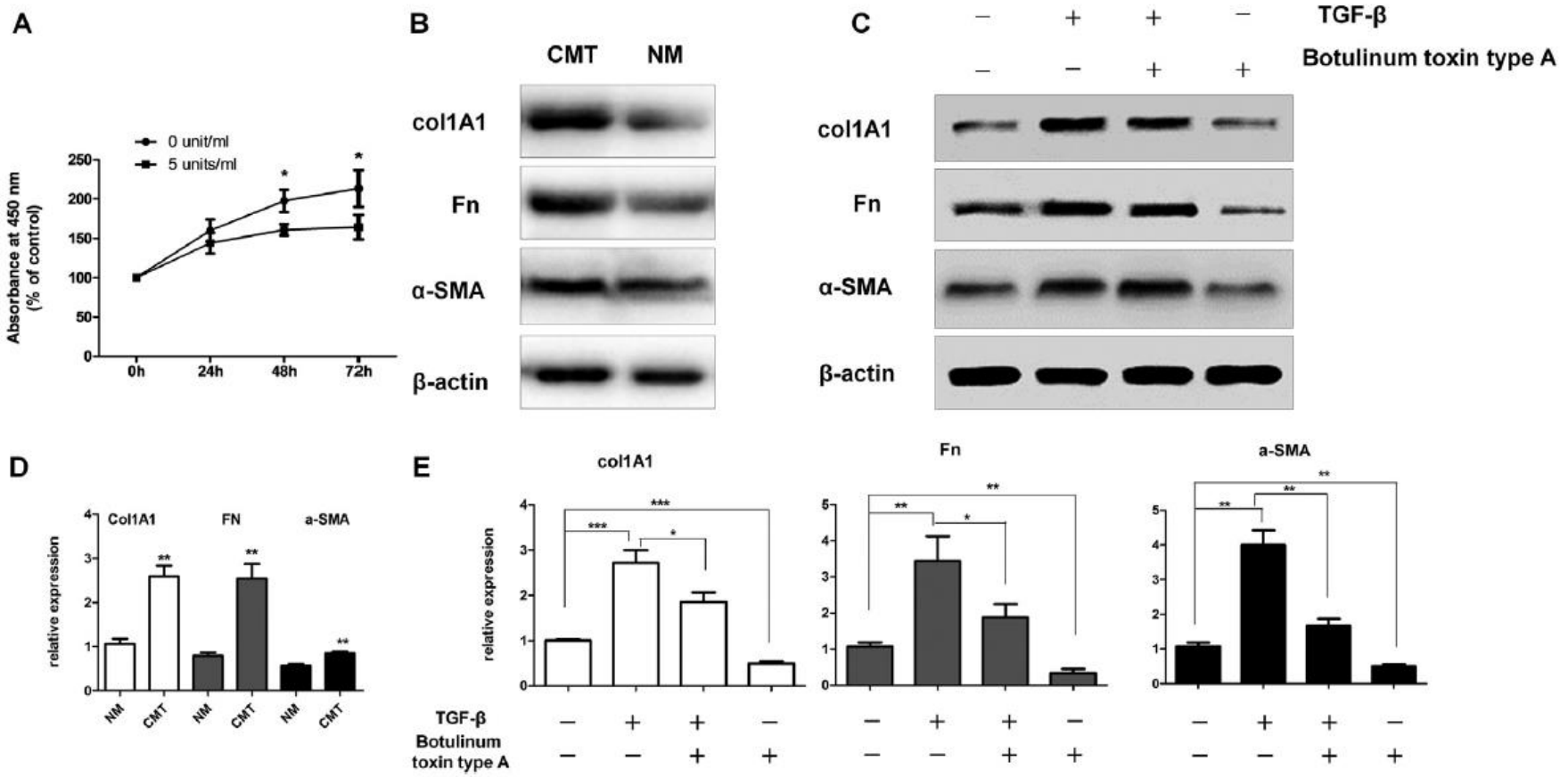
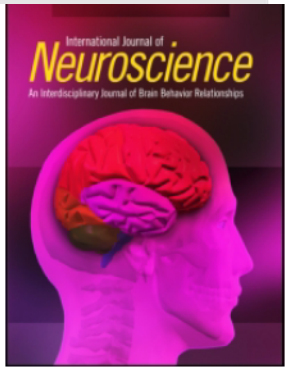


Fig. 5. BTA inhibits the proliferation of fibroblasts, fibroproliferative expression and myofibroblast differentiation in NIH3T3 fibroblasts. (A) *Dots* represent untreated cells, and squares represent cells treated with 5 units/ml BTA. Western blot and qPCR were used to analyze the protein (B) and mRNA (D) expression of Col1A1, Fn and α-SMA between CMT tissue and the matched normal muscle. (C) The expression of Col1A1, Fn and α-SMA was detected by western blot with TGF-β (10 ng/ml), BTA (5 units/ml) in NIH3T3 fibroblasts. (E) The mRNA expression of Col1A1, Fn and α-SMA was detected by qPCR with TGF-β (10 ng/ml), BTA (5 units/ml) in NIH3T3 fibroblasts. Data are presented as means ± SD; Error bars = SD; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.0001$.

In conclusion, BTA has potential therapeutic effect on anhydrous alcohol induced CMT model, and its mechanism of improving CMT may be related to reduce the ECM formation by suppressing protein expression of α-SMA and regulating the proliferation of fibroblast.



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Effects of botulinum toxin A therapy and multidisciplinary rehabilitation on lower limb spasticity classified by spastic muscle echo intensity in post-stroke patients

Takatoshi Hara, Masahiro Abo, Hiroyoshi Hara, Kazushige Kobayashi, Yusuke Shimamoto, Yamato Shibata, Nobuyuki Sasaki, Naoki Yamada & Masachika Niimi

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Objectives: The purpose of the present study was to investigate retrospectively the relationship between botulinum toxin type A plus multidisciplinary rehabilitation and muscle echo intensity in post-stroke patients with spasticity. The primary aim was to investigate whether the effects of the intervention on the improvement of spasticity depend on muscle echo intensity, and the secondary aim was to investigate whether the motor function of the lower limbs depends on muscle echo intensity.

Methods: A 12-day inpatient protocol was designed for 102 post-stroke patients with spasticity due to lower limb paralysis. Muscle echo intensity of the triceps surae muscle was measured by ultrasonography, and the patients were categorized into four groups based on Heckmatt scale grades (Grades I–IV).

Results: All four groups classified by the Heckmatt scale showed significant pre-to-post-intervention differences in the knee and ankle modified Ashworth scale scores ($p < 0.05$). Grades I–III patient groups showed a significant improvement in lower limb motor function following intervention. Grade IV patients did not show a significant improvement in lower limb motor function.

Conclusions: We observed significant improvements in the modified Ashworth scale scores after botulinum toxin type A and multidisciplinary rehabilitation therapy on post-stroke patients with spasticity. Although patients with lower muscle echo intensity demonstrated improvements in motor function, the improvement was poor in those with higher muscle echo intensity.

Table 1. Subject data.

	All patients ($n = 102$)	Grade I ($n = 17$)	Grade II ($n = 55$)	Grade III ($n = 24$)	Grade IV ($n = 6$)	*P* value
Age at injection, years (SD)	63.0 (13.4)	55.25 (8.4)	64.1 (10.6)	65.6 (10.1)	56.6 (14.2)	<0.05
Male/female, *n* (%)	78 (76.4)/24 (23.6)	16 (94.1)/1 (5.9)	44 (80.0)/1 1(20.0)	15 (62.5)/9 (37.5)	3 (50.0)/3 (50.0)	n.s.
Type of stroke, *n* (%)						
Cerebral infarction	37 (36.2)	2 (11.7)	24 (43.7)	10 (41.6)	1 (83.3)	
Intracerebral hemorrhage	63 (61.7)	14 (82.5)	31 (56.3)	13 (54.4)	5 (16.7)	
Subarachnoid hemorrhage	2 (2.1)	1 (5.8)	0 (0.0)	1 (4.0)	0 (0.0)	
Side of hemiparesis						
Rt/Lt, *n* (%)	48 (46.0)/54 (54.0)	6 (35.2)/11 (64.8)	27 (49.0)/28 (51.0)	13 (54.2)/11 (45.8)	2 (33.3)/4 (66.7)	n.s.
Brunnstrom recovery stage, median (IQR)						
Lower limb	4 (1)	4 (1)	4 (1)	4 (1)	4 (1)	n.s.
Distribution of the muscles in the highest HMS grade						
Gc-L/Gc-M/So		100/100/100	100/96.3/56.3	100/83.3/87.5	83.3/100/50.0	
Time between onset and treatment, days (SD)	2308.5 (2368.7)	3572.75 (4721.6)	1806 (1392.8)	2508.8 (1491.6)	2826.5 (2535.3)	n.s.

Note: SD, standard deviation; n.s., not significant; Rt, right; Lt, left; IQR, interquartile range; Gc-L, gastrocnemius lateral; Gc-M, gastrocnemius medial; So, soleus.

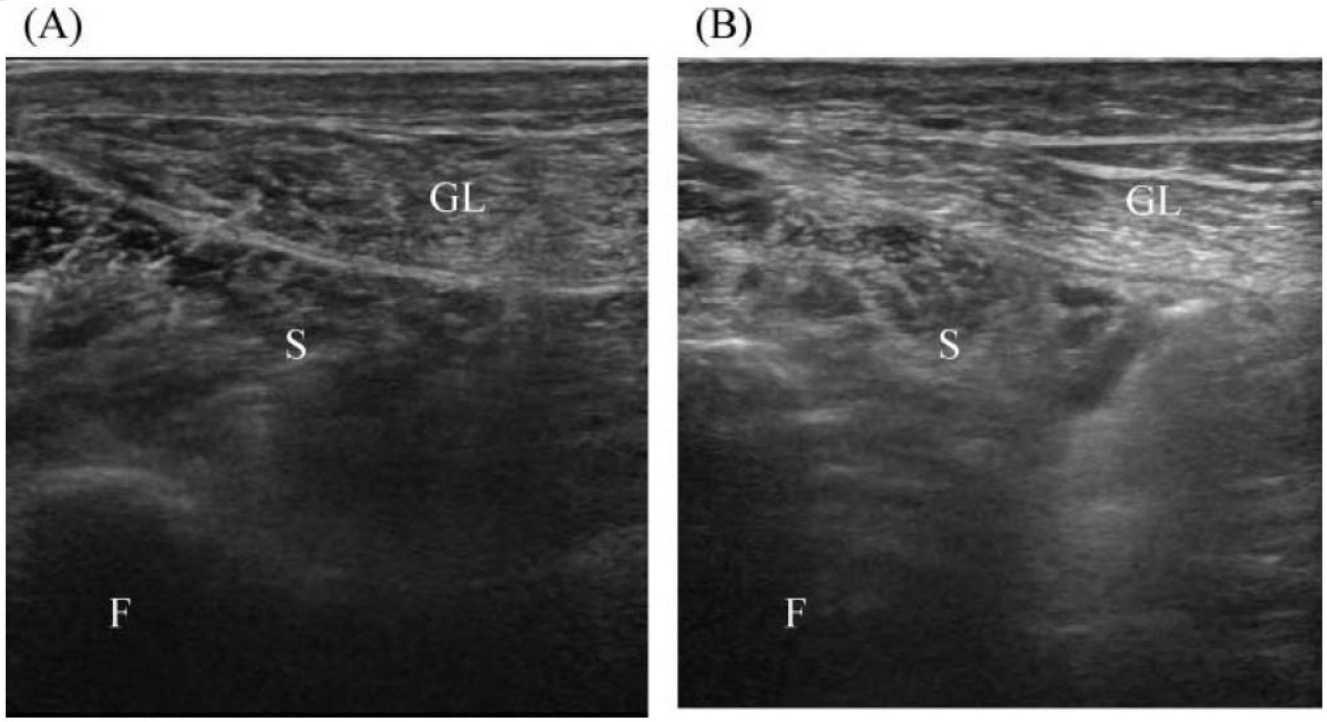

Figure 2. Ultrasonography imaging (transverse view) of the gastrocnemius and soleus muscles of patients with Heckmatt scale Grade II (A) and Heckmatt scale Grade III (B). F: fibula; GL: gastrocnemius lateralis; S, soleus.

Table 3. Change in the assessment values between admission and discharge.

	Grade I ($n = 17$)		Grade II ($n = 55$)		Grade III ($n = 24$)		Grade IV ($n = 6$)	
	At Admission	At Discharge	At Admission	At Discharge	At Admission	At Discharge	At Admission	At Discharge
Brunnstrom recovery stage, median (IQR)								
Lower limb	4 (1)	4 (1)	4 (1)	4 (1)	4 (1)	4 (1)	4 (1)	4 (1)
MAS, median (IQR)								
Knee extension	1 (0.5)	0 (0.5)*	1 (0.5)	1 (1)*	1.5 (1)	1 (1.5)*	1.5 (1)	1 (1.5)*
Ankle dorsiflexors	1.5 (1)	1 (1)*	1.5 (1.5)	1 (0.5)*	2 (0.5)	1.5 (1)*	1.75 (0.5)	1 (0.375)*
ROM, angle, median (IQR)								
Hip flexion	105 (11.25)	110 (15)*	110 (11.25)	110 (5)*	105 (6.25)	110 (15)	112.5 (8.25)	117 (12.5)
Knee extension	0 (0)	0 (0)	−5 (5)	−5 (5)	0 (1.25)	0 (2.5)	0 (0)	0 (0)
Ankle dorsiflexion	−5 (13.5)	0 (2.5)*	−5 (10)	5 (10)*	−5 (10)	0 (10)*	−5 (3.75)	−5 (2.5)
10MWT, s, median (IQR)	13.9 (9.68)	13.8 (5.6)	21.38 (18.9)	19.5 (20.3)*	21.6 (23.5)	19.7 (26.4)*	15.0 (4.4)	15.9 (8.4)
FRT, cm, median (IQR)	22 (5.5)	23.5 (3.5)	20 (10.1)	24 (9)*	20 (7.6)	22 (7)*	20.1 (13.7)	19.5 (13)
TUG, s, median (IQR)	16.6 (12.4)	16.3 (7.3)*	23.2 (24.9)	22.0 (20.13)*	23.2 (19.7)	22.5 (19.8)*	16 (6.6)	21.5 (16.6)

Note: IQR, interquartile range.
*Statistically significant difference between admission and discharge ($p < 0.05$).

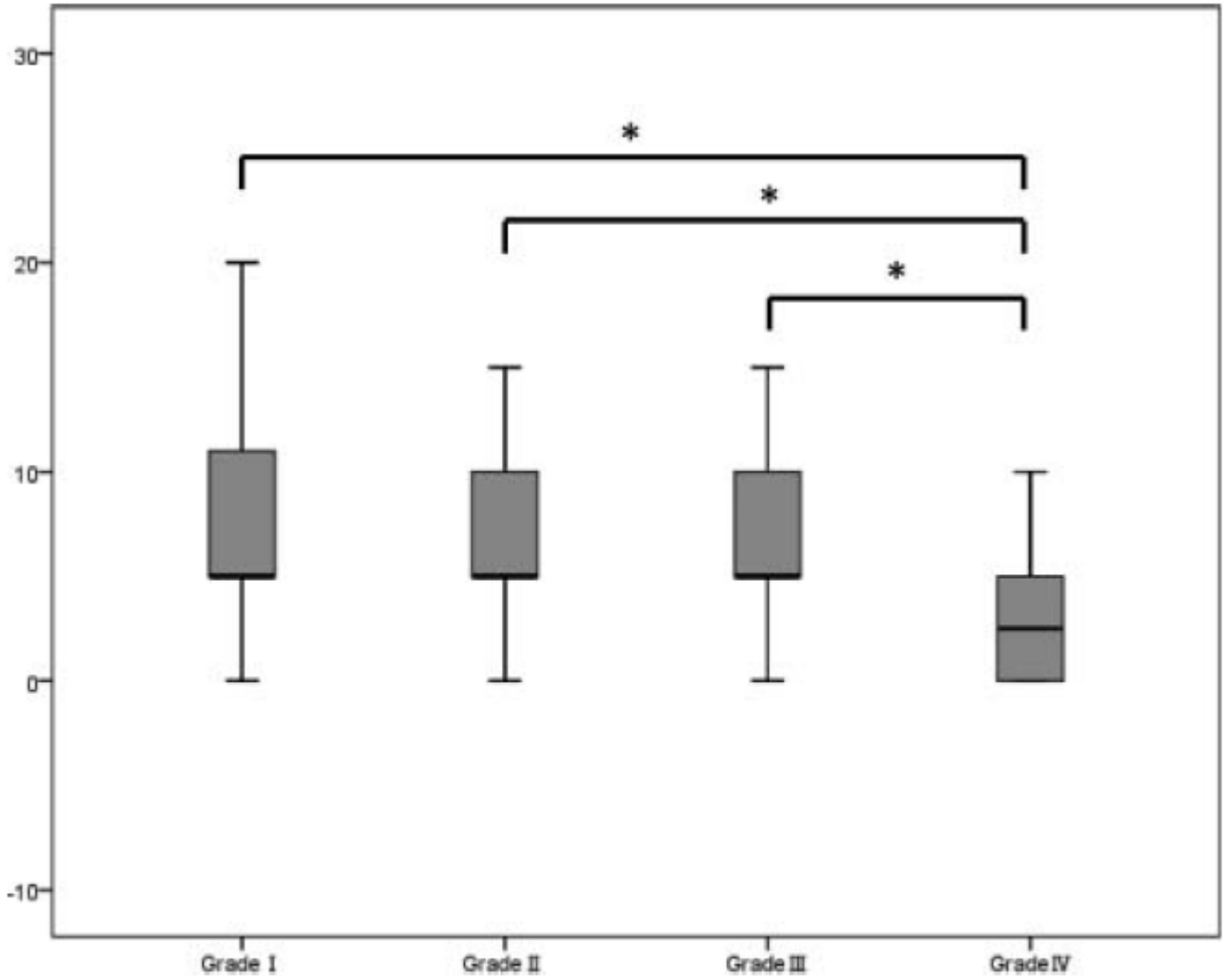

Figure 3. Changes in ankle dorsiflexion range of motion before and after intervention. Significant inter-group differences were found between the Grade I, II and III groups and the Grade IV group ($^{*}p < 0.05$).

Conclusion

We investigated the relationship between muscle echo intensity and combined BoNT-A and MD-Re therapy in post-stroke patients with spasticity. Statistically significant changes were observed in the MAS scores after intervention. However, patients with low muscle echo intensity demonstrated an improvement in motor function, whereas those with high muscle echo intensity showed poor motor function improvement.

МЕТОДИКИ

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https://doi.org/10.1007/s00415-018-8819-6

ORIGINAL COMMUNICATION

Personalized botulinum toxin type A therapy for cervical dystonia based on kinematic guidance

Olivia Samotus[1,2] · Jack Lee[1] · Mandar Jog[1,2]

Results For the "kb" participants, there was a significant 28.8% (− 11.25 points) reduction in TWSTRS total score at week 6, as well as significant reduction in severity and disability TWSTRS sub-scores (parts I and II) with maintained improvement at subsequent visits. As for the "vb" participants had a significant reduction in total TWSTRS score by 28.5% (− 9.84 points) after week 22. Disability score for the "vb" group trended towards improvement over 38 weeks.

Conclusion Clinical judgement guided by kinematic analysis of CD biomechanics can result in faster optimal muscle selections and minimize use of higher BoNT-A doses as compared to visual determination, thereby achieving comparable and potentially better treatment outcomes.

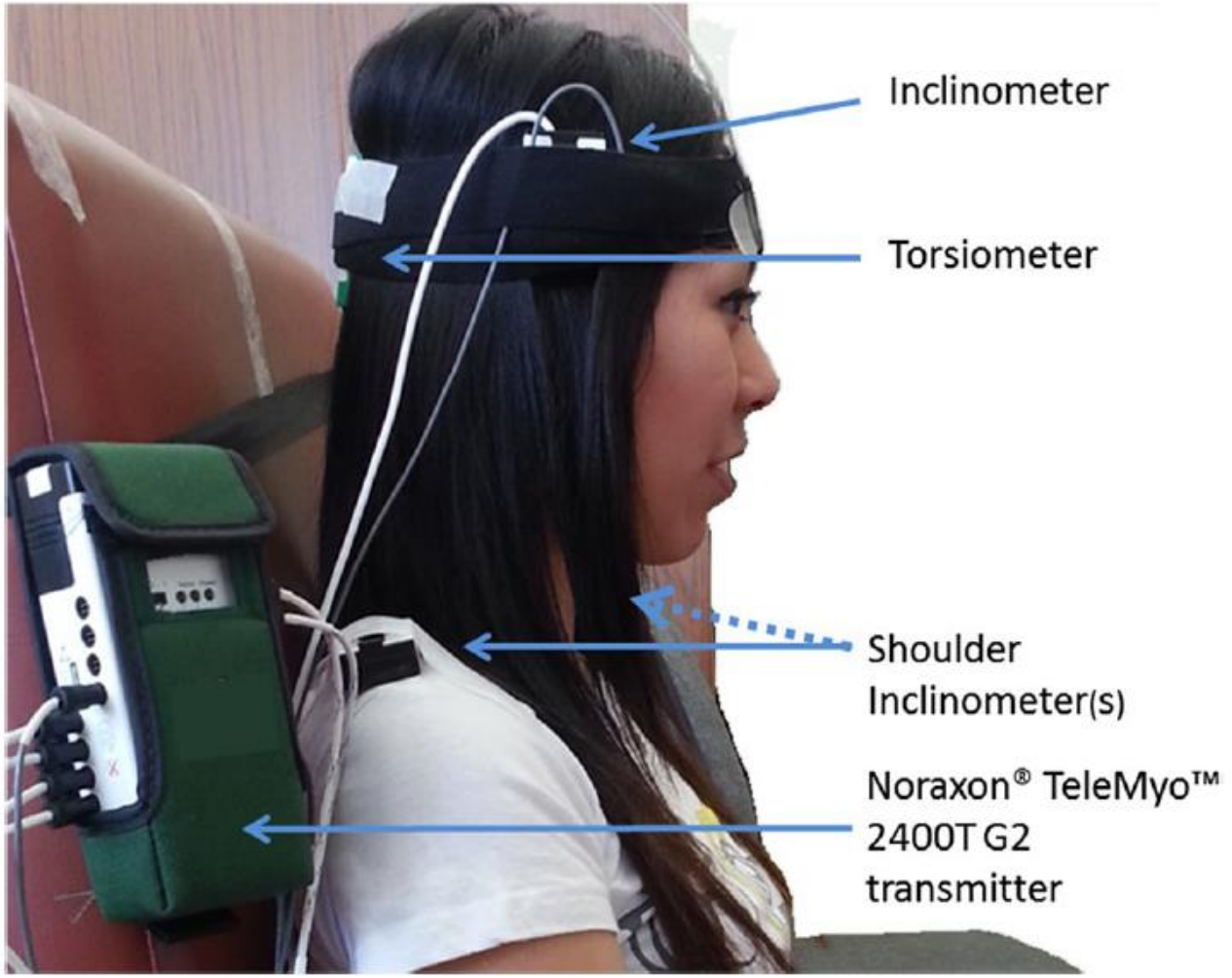

Fig. 1 Motion sensor placement to capture multiaxial head/neck movements for each participant while in the seated position with their eyes open. A Norxaon TeleMyo™ 2400T G2 transmitter was used to capture information from one torsiometer, placed at C2 and T2 spinal segments, and from three inclinometers, placed at the right temple, and one on each shoulder

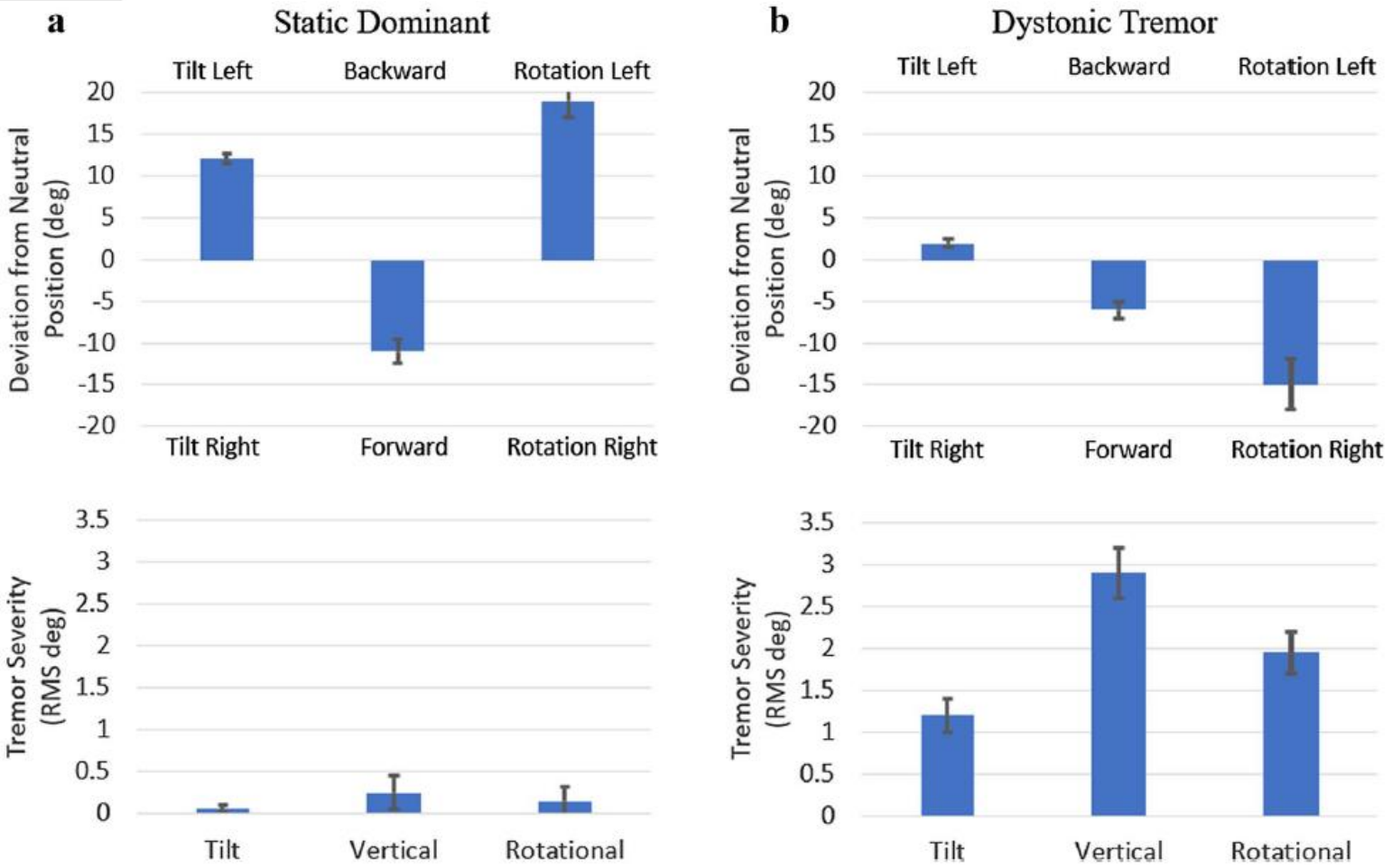

Fig. 2 Sample kinematic assessment results for two participants with static dominant dystonia (**a**) and with dystonic tremor dominance (**b**). The top plots represent the severity of static dystonia in each degree of freedom, lateral tilts, vertical (backward/forward) and rotational movements. The bottom plots represent the presence and severity of dynamic, tremor movements in each degree of freedom

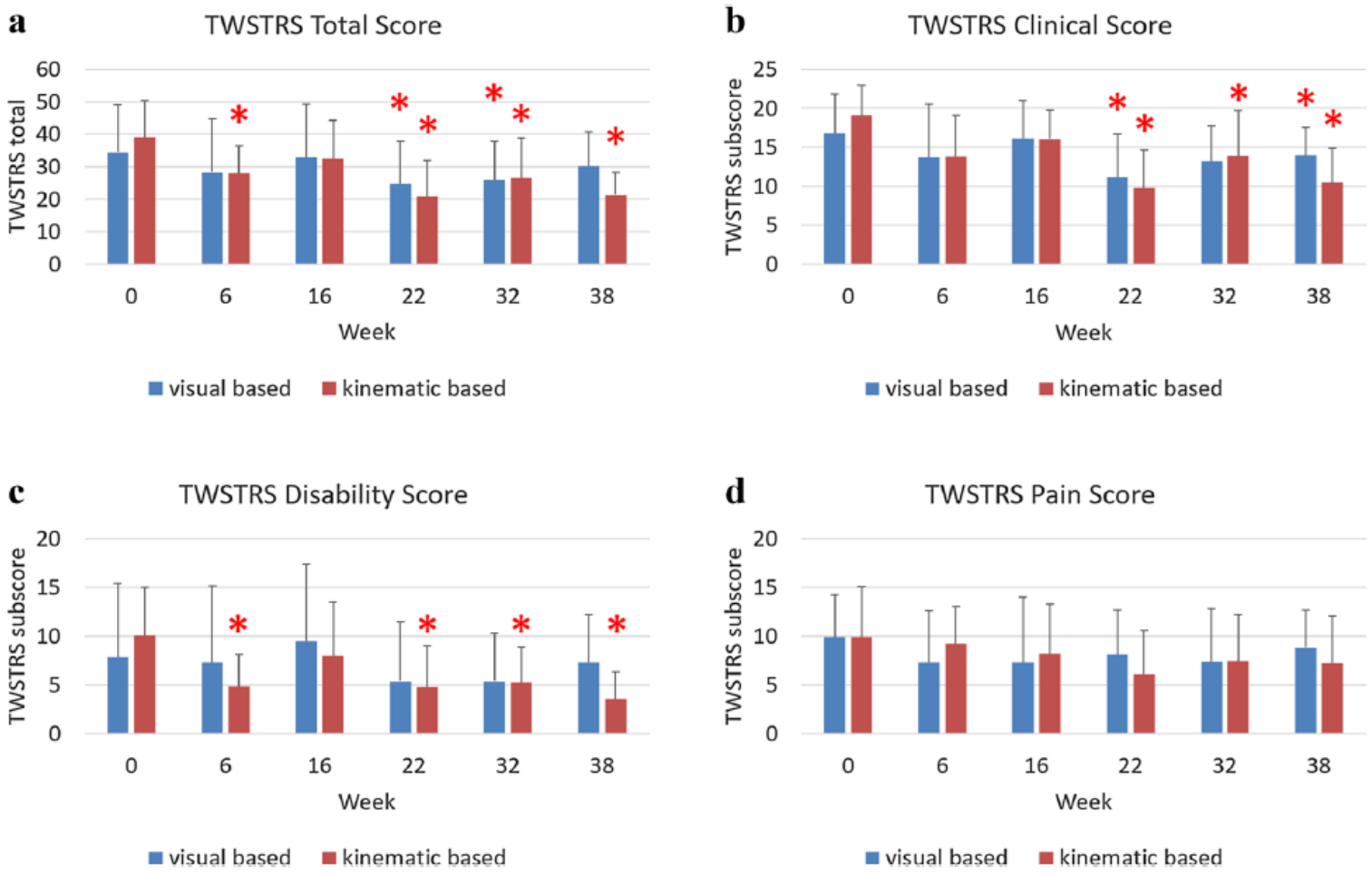

Fig. 3 Changes in the mean TWSTRS total score (**a**), part I sub-score for CD severity (**b**), part II sub-score for CD-associated disability (**c**), and part III sub-score for pain (**d**) both visual- and kinematic-based treatment groups. Asterisks represent statistical significant differences ($p < 0.05$) compared to week 0

Predictive Techniques for Neurotoxin Outcomes

Liza Brown, DO,* Drew Taylor, MD,† and Eduardo Weiss, MD, FAAD‡

Dermatol Surg 2018;44:721–725

BACKGROUND Botulinum-derived neurotoxins have become a substantial tool in dermatologists' armamentarium for facial/neck rejuvenation. Current literature discusses anatomical "danger zones" to avoid during neurotoxin injection to prevent brow ptosis, blepharoptosis, and lower facial ptosis.

OBJECTIVE The aim of this study was to determine whether lidocaine 1% local anesthetic can be used to predict botulinum toxin treatment outcomes and prevent adverse effects of unwanted paralysis.

MATERIALS AND METHODS One percent lidocaine was drawn up using BD ultra-fine 31 G (5/16″), 0.5-mL insulin syringes in the same quantity that would be drawn up for neurotoxin placement. The patient's face was cleansed and mapped; 0.1 mL of 1% lidocaine was injected × 5 sites in the glabella; and 3 sites were injected with 0.05 mL in the frontalis. The patient was assessed after 10 minutes.

RESULTS Improvement in frontalis and glabellar rhytides was appreciated, with noted "spocking" of the lateral brows. This technique allowed the authors to visualize the need for placement of toxin more laterally with eventual successful predictive placement for neurotoxin.

CONCLUSION This technique of using local 1% lidocaine allows the practitioner to devise a neurotoxin distribution map tailored for each patient to limit unwanted paralysis from improper neurotoxin placement.

Figure 5. Final successful predictive placement of neurotoxin after 1% lidocaine injection with resolution of spocked brows (comparison to before photographs [Figure 1]).

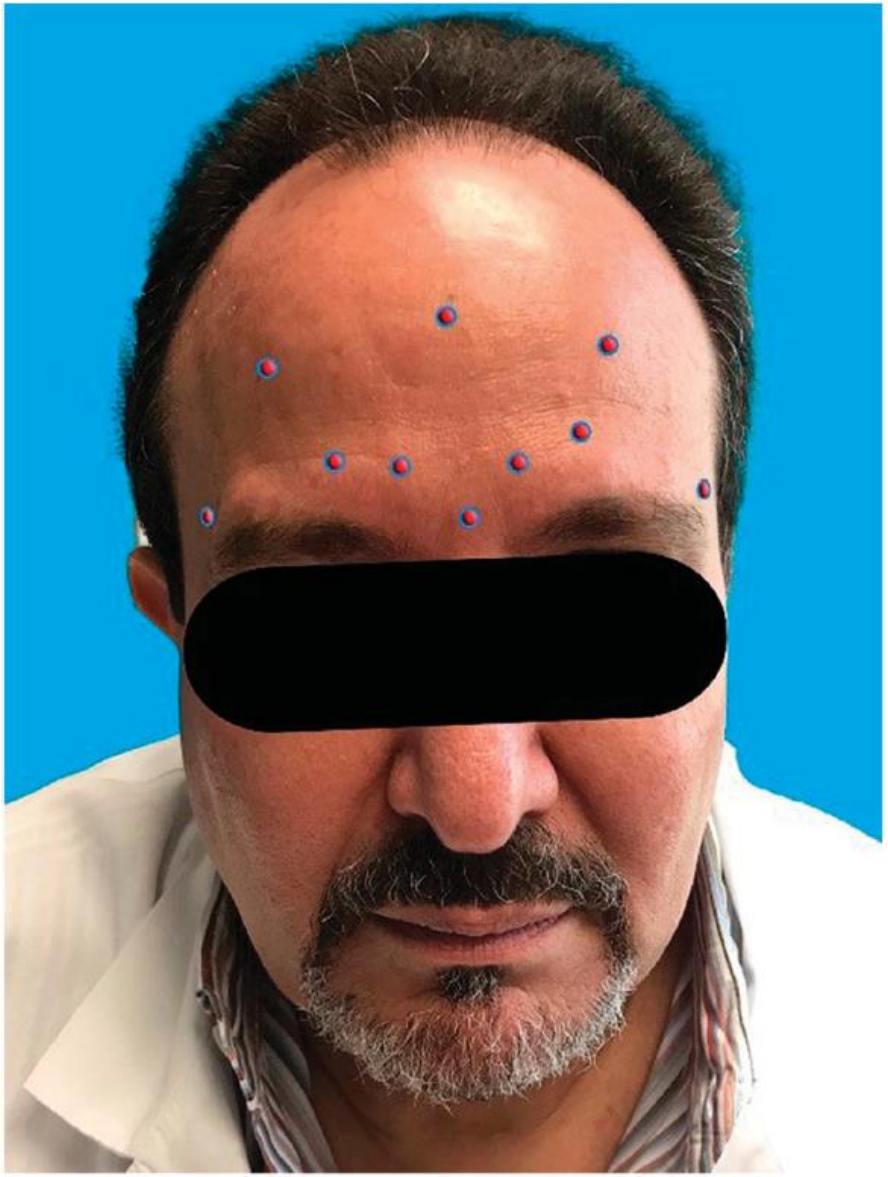

Figure 6. Patients' specific anatomical map for future successful neurotoxin placement.

injection of the lower frontalis, and to keep injections 1

A novel, noninvasive anesthetic method for neurotoxin injection for palmar hyperhidrosis

Lauren Lam, BScH, MD,[a] and Susan Poelman, MSc, MD, FRCP(C), DABD[b]
Edmonton and Calgary, Canada

J Am Acad Dermatol
April 2018

This PowerPoint Template has clean and neutral design that can be adapted to any content and meets various market segments. With this many slides you are able to make a complete PowerPoint Presentation that best suit your needs.

A frozen, 1/4-inch thick, flat steel plate gripped for ~30 seconds provides effective anesthesia for neurotoxin injection to the palms (Fig 1). The plate is easily adjusted as the injections progress in a grid-like pattern. Several plates can be frozen ahead of time and replaced as needed as the plate warms. They can be autoclaved between patients and are readily available at a local hardware store.

This method helps reduce discomfort, is cost-effective, has quick onset of anesthesia, and avoids the side effects of anesthetic medications and the dripping of melted ice.

In summary, this is an inexpensive, useful, and elegant method for achieving pain control in patients treated with palmar botulinum toxin injections. It is well received by patients and improves their quality of life by allowing them to tolerate these injections at regular intervals.

Fig 1. Method of anesthesia for patient with palmar hyperhidrosis. An 8 × 5 × 0.5–cm frozen steel plate can fit in the patient's palm and can be adjusted as needed during neurotoxin injections given in a grid-like pattern.

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European Journal of Physical and Rehabilitation Medicine 2018 June;54(3):469-85
DOI: 10.23736/S1973-9087.17.04664-0

SPECIAL ARTICLE

Sonographic guide for botulinum toxin injections of the upper limb: EUROMUSCULUS/USPRM spasticity approach

Murat KARA [1] *, Bayram KAYMAK [1], Alper M. ULAŞLI [2], Fatih TOK [3], Gökhan T. ÖZTÜRK [2], Ke-Vin CHANG [4], Ming-Yen HSİAO [4], Chen-Yu HUNG [5], Arzu YAĞIZ ON [6], Levent ÖZÇAKAR [1]

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European Journal of Physical and Rehabilitation Medicine 2018 June;54(3):486-98
DOI: 10.23736/S1973-9087.17.04667-6

SPECIAL ARTICLE

Sonographic guide for botulinum toxin injections of the lower limb: EUROMUSCULUS/USPRM spasticity approach

Bayram KAYMAK [1], Murat KARA [1] *, Fatih TOK [2], Alper M. ULAŞLI [3], Gökhan T. ÖZTÜRK [3], Ke-Vin CHANG [4, 5], Ming-Yen HSİAO [4], Chen-Yu HUNG [5], Arzu YAĞIZ ON [6], Levent ÖZÇAKAR [1]

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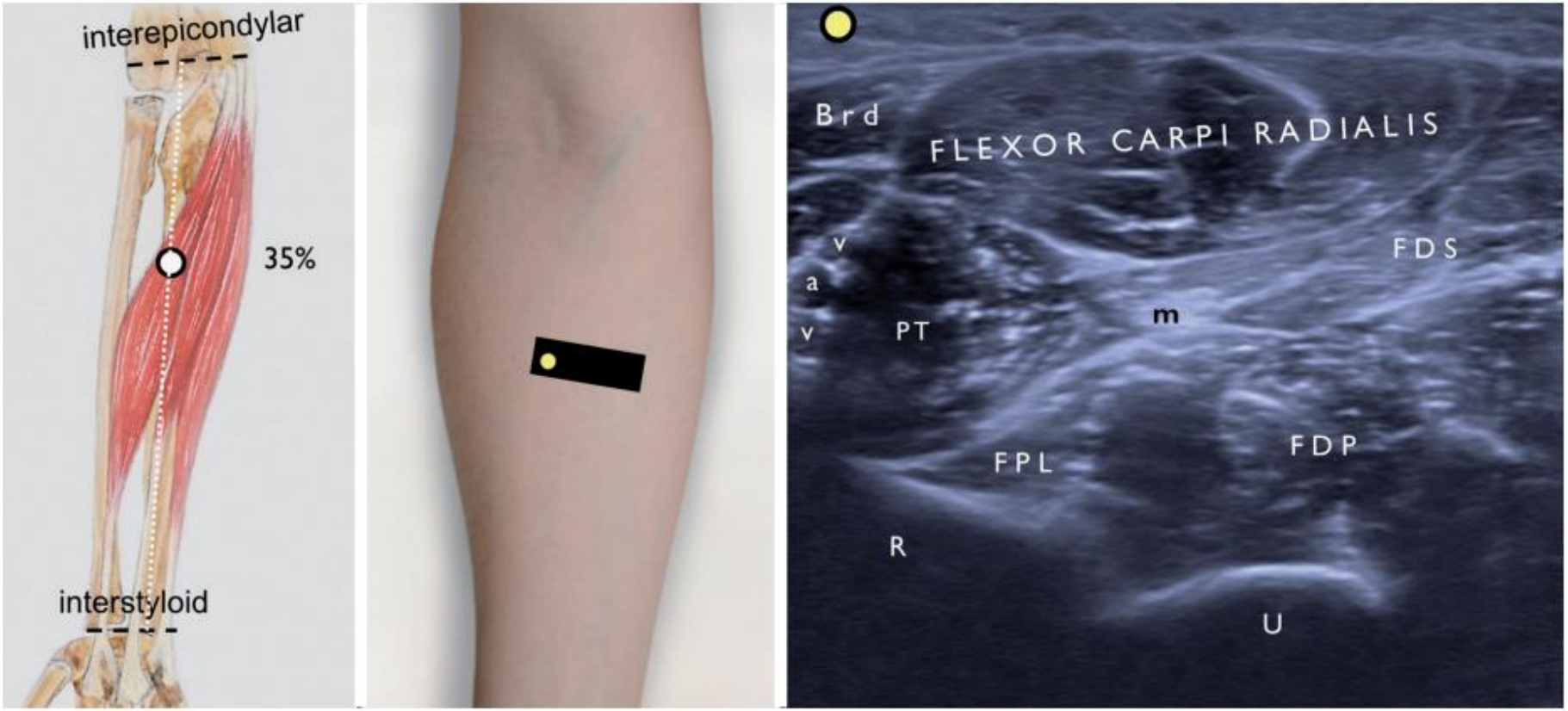

Figure 13.—Flexor carpi radialis muscle.
R: radius; U: ulna; a: radial artery; v: vein.

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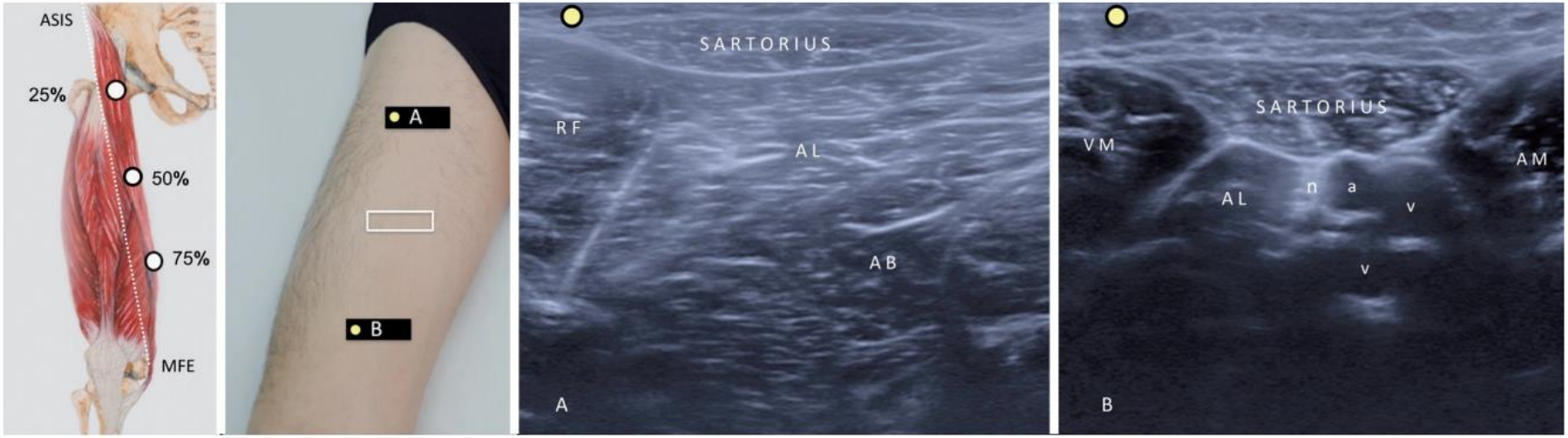

Figure 3.—Sartorius muscle.
ASIS: anterior superior iliac spine; MFE: medial femoral epicondyle.

Материалы

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