Botulinum Treatment for Post-stroke Spasticity: Low Dose Regime

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Abstract

The purpose of this study was to investigate the effects of botulinum A toxin for the treatment of post-stroke spasticity patients. Twenty two post-stroke spasticity patients were recruited in the study. All patients had moderate to severe spasticity of upper and lower extremities. Botulinum toxin was injected intramuscularly according to the spasticity pattern. Injections were performed at either 2, 3, or 6 month intervals as determined by the neurologist. The total dose of each session of injection varied between 50-100 IU. Subjective and objective examinations were conducted by the physiotherapist prior to the first injection and subsequently at 1st week, 2nd week and every month after each injection. All patients were asked subjectively about their satisfaction with the treatment. The objective examinations used in this study were Ashworth scale and Fugl-Meyer Sensorimotor Assessment Form. All patients were satisfied with the treatment. Marked reduction of the spasticity was found after one to two weeks of injection. The duration of effectiveness of botulinum toxin for spasticity is from 3-6 months. The average improvement in Ashworth score was between 1 and 1.5 points. The Fugl-Meyer scores showed significant improvement in most patients for the motor function of upper and lower extremities, and balance. All patients demonstrated increase in passive range of joint motion and decrease in joint pain.

This study demonstrates that botulinum toxin therapy is safe and effective in treating chronic upper and lower extremities' spasticity following stroke. The dosage used in this study is about one-half of the recommended dosage in the literature. The only drawback of this therapy is its high cost (300 US dollars for 100 I.U.).

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Spasticity is a complex disorder of excess muscle tone. The etiology and pathophysiological mechanisms of spasticity are varied. Classically, it is considered that there is a loss of descending inhibitory influences resulting in increased excitability of dynamic fusimotor (gamma) neurons and alpha motor neurons. Spasiticity may accompany diffuse or localised cerebral or spinal pathology. Stroke is one of the most common causes of spasticity in general practice which causes significant disability in affected patients[1,2].

A variety of treatment methods are used in an attempt to decrease spasticity in stroke patients. Some of these methods are physical therapy, and antispasticity oral medication i.e. dantrolene sodium, diazepam, baclofen. The use of antispasticity oral medication is usually considered after the more conservative treatment approaches have been tried. Currently, available treatment modalities are often of limited benefit, particularly in chronic stroke patients with moderate to severe spasticity.

Botulinum toxin (a presynaptic blocker of acetylcholine release) has been used to treat a variety of disorders of excess muscle activity such as strabismus, blepharospasm, cervical dystonia, spasmodic torticollis and spasticity in cerebral palsy[3-8]. Thus it is a good rationale to treat post-stroke spasticity with botulinum toxin.

The purpose of this study was to investigate the effects of using botulinum toxin for the treatment of post-stroke spasticity patients.

METHODS

Procedure

A longitudinal open-study of 22 post-stroke spasticity patients treated with botulinum A toxin injection was conducted at Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand from September 1994 to January 1998. Botulinum toxin was injected intramuscularly according to the spasticity pattern. Injections were performed at either 2, 3 or 6 month intervals as determined by the neurologist. Patients were assessed prior to the first injection and subsequently at 1st week, 2nd week and every month after each injection. The subjective and objective examinations were performed by a physiotherapist. All patients were asked subjectively about their satisfaction with the treatment. The severity of spasticity was assessed by using Ashworth scale (Appendix I). The objective examination used in this study was a Fugl-Meyer Sensorimotor Assessment Form. It included motor function scores of upper extremity (64 points), motor function scores of lower extremity (32 points), scores of balance (14 points), scores of passive joint motion (44 points) and scores of joint pain during passive movement (44 points). The details of each item are presented in Appendix II.

Data Analysis

The Wilcoxon Match-Paired Sign-Rank test was used to determine the difference in Fugl-Meyer scores between pre-treatment of the first injection and post-treatment of the last injection. The statistically significant difference was set at p-value less than 0.05. All data analyses were performed using the SPSS version 6.0 statistical package.

RESULT

The patients' charateristics are summarised in Table 1. Fourteen male and eight female post-stroke patients were included in the study. The mean age was 63.91±10.28 years (range 43 to 84 years). Eleven patients had left and eleven had right side strokes. The duration of suffering from spasiticity prior to treatment of each patient ranged from 6 months to 17 years. All patients had moderate to severe spasticity of upper and lower extremities as determined from Ashworth Scale.

Table 1. Patients characteristics.

Variable	Mean	Range
Age (years)	63.91±10.28	43-84
Duration from onset to the first treatment (months)	57.77±52.30	6-204
Number of treatments	4.95±3.09	1-12

One hundred and nine sessions of botulinum toxin treatment were given to 22 post-stroke spasticity patients. The most commonly selected muscles of upper and lower extremities for injection are shown in Table 2. The total dose of each session of injection varied between 50 and 100 IU which depended on the number of muscles injected. All patients were satisfied with the treatment.

Table 2. Commonly selected muscles for injection in spasticity patients.

Muscles	Dose
Upper extremity	
Biceps brachii	30-40 I.U.
Flexor carpi ulnaris	15-20 I.U.
Flexor carpi radialis	15-20 I.U.
Flexor digitorum profundus	15-20 I.U.
Supinator	15-20 I.U.
Brachioradialis	15-20 I.U.
Pronator	15-20 I.U.
Lower extremity	
Adductor magnus	40-60 I.U.
Hamstrings	20-40 I.U.
Gastrocnemius	40-60 I.U.

The severity of spasticity evaluated from Ashworth scale showed marked decrease of muscle tone for the injected muscles particularly after one to two weeks of the injection in all patients. The results demonstrated a decrease in Ashworth score of 1.5-2 points for both upper and lower extremities. Sixty eight per cent of the patients (15 out of 22) demonstrated a marked reduction of spasticity within one month. The duration of effectiveness of botulinum toxin for spasticity is from 3-6 months. The average improvement in Asworth score was between 1 and 1.5 points.

The objective assessment from Fugl-Meyer scores showed significant improvement in most patients. The major finding evident from the Fugl-Meyer scores was that some patients had no improvement of upper extremity (3 patients), lower extremity (4 patients) and balance (2 patients), whereas for joint motion and joint pain, all patients improved. For each item of the Fugl-Meyer assessment, the change in Fugl-Meyer score from the first treatment (pre-treatment) to the last treament (post-treatment) was statistically significantly different ($p < 0.01$). Table 3 outlines specific details for each item, and presents median values and ranges of Fugl-Meyer scores on all five items.

Figures 1 to 4 show the number of patients suffering from joint pain during passive motion before the first treatment (pre-treatment) and after the last treatment (post-treatment). Marked improvements were seen in the shoulder flexion, elbow extension, wrist extension and shoulder abduction for upper extremity. For the lower extremity, Marked improvements were seen in the ankle dorsiflexion, hip internal rotation, knee extension, foot supination and hip external rotation.

DISCUSSION

Botulinum toxin injection into the spastic muscles produced significant improvements in the muscle tone and motor functions as shown by objective outcome measures. All patients reported satisfaction with the treatment, in particular with the reduction of muscle tone and joint pain during passive motion. This study found an average improvement in Ashworth scores of 1-1.5 points which is clinically significant and consistent with the study of Yablon et al[9]. Yablon et al conducted an open-label trial on 21 subjects with traumatic brain injury who had spastic hypertonic in the upper extremity and had not responded to conservative treatments. They found an increase on the Ashworth score of 1.5 points after injection.

Table 3. Changes in Fugl-Meyer Scores for upper extremity, lower extremity, balance, joint motion and joint pain.

	Upper extremity (64)	Lower extremity (32)	Balance (14)	Joint motion (44)	Joint pain (44)
Pre-treatment					
Median value	11	10	7.5	31.5	30.5
Range	4-32	4-21	0-11	19-40	10-40
Post-treatment					
Median value	15.5	14	10	39.5	41
Range	4-55	4-29	0-12	24-44	26-44
p-value*	0.0001	0.0002	0.0003	0.0001	0.0001

*p-value from Wilcoxon Match-Paired Signs- Ranks test

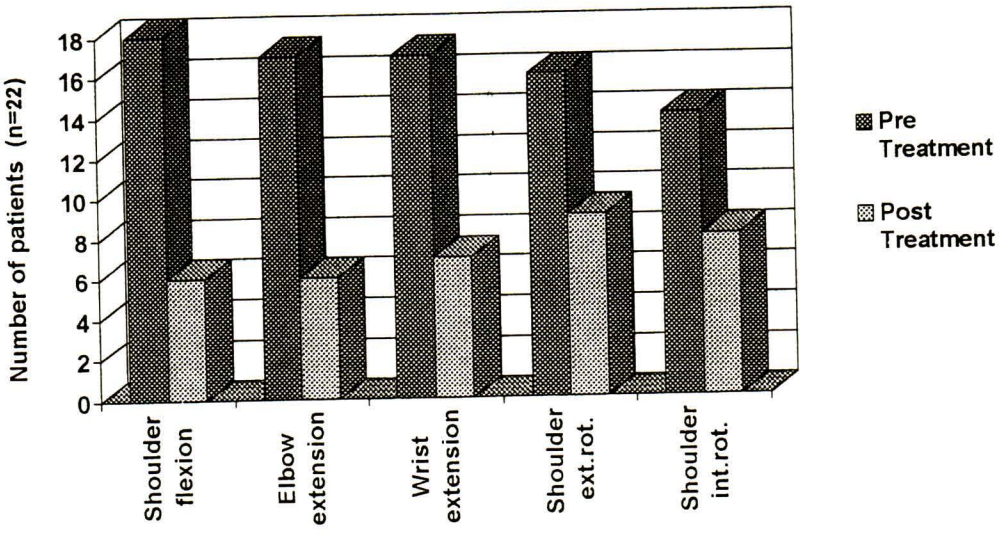

Fig. 1. Number of patients suffering from joint pain of upper extremity.

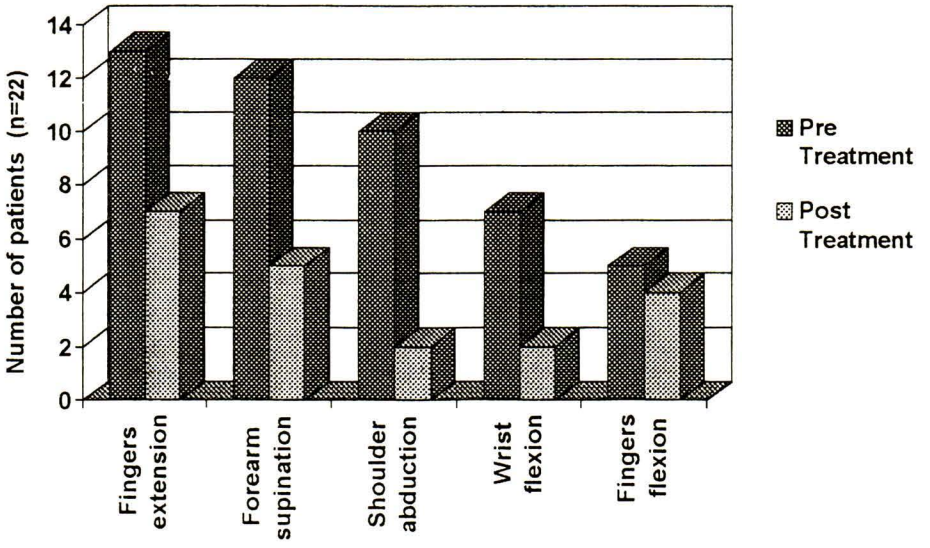

Fig. 2. Number of patients suffering from joint pain of upper extremity (continued).

Most patients also reported that after a few injections they had improved their resting limb position, for example, less elbow flexion in a standing position, less hip adduction in a supine position or less knee flexion in a supine or sitting position. In two patients with severe spasticity of wrist and fingers flexion, and forearm pronation, the injection of botulinum toxin into selected muscle groups led to improved hygiene and increased ease of care. The objective evidence of Fugl-Meyer scores demonstrated the significant improvements of all five items and supported the findings of subjective examination.

The possible adverse effects of botulinum toxin injection may be divided into four parts; generalized discomfort, local effect, undesirable

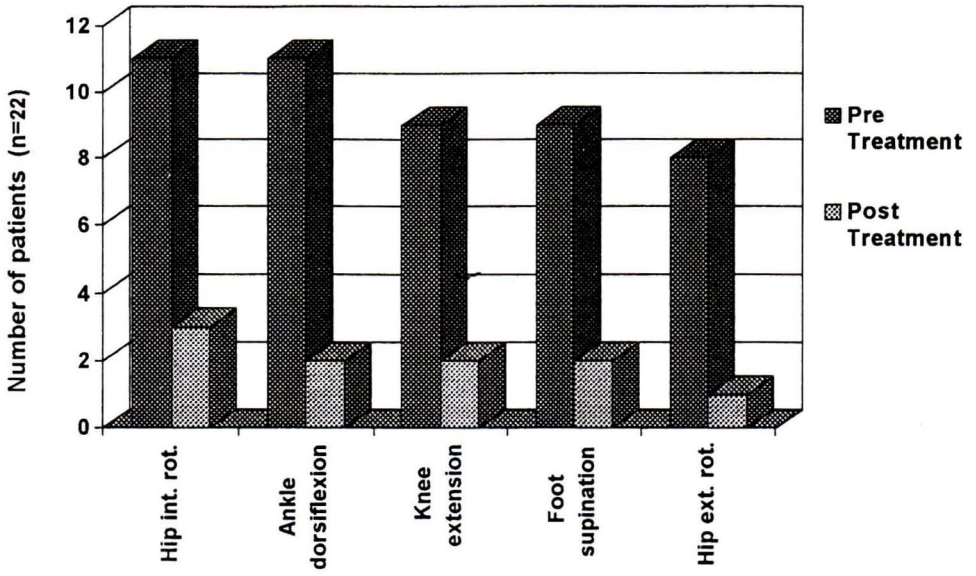

Fig. 3. Number of patients suffering from joint pain of lower extremity.

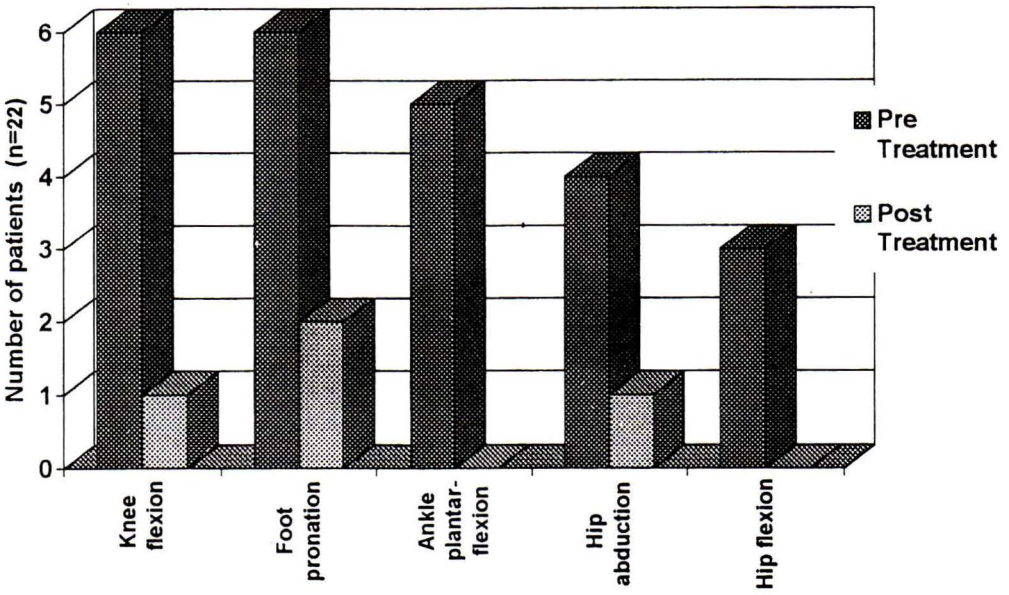

Fig. 4. Number of patients suffering from joint pain of lower extremity (continued).

muscular weakness and immune reaction[6,10]. The generalized discomforts include fatigue, malaise, headache, dizziness, nausea and flu-like symptoms. The local adverse effects include local pain and ecchymoses around the injection sites. Undesirable muscular weakness can occur if botulinum toxin diffuses into unselected muscles. For the immune reaction, the development of resistances have been reported approximately 5 per cent. This could reduce the effectiveness of botulinum toxin.

The site of action of botulinum toxin is at the nerve terminal. Botulinum toxin attaches to presynaptic neurons and inhibits the release of acetylcholine[11]. A high dose of botulinum toxin may cause temporary paralysis of the muscles[12].

The use of botulinum toxin in this study demonstrated that no ill or side effects occurred in any patient. The dosage employed for each muscle in this study was less than the other studies(9,13, 14). Thus both safety and efficacy for botulinum toxin treatment in post-stroke spasticity patients were affirmed. However, some muscle atrophy at the injected site could be observed by the researchers.

Botulinum toxin injections have become the choice of treatment for dystonias in several parts of the body including limb spasticity. With appropriate selection of muscle for injection, botulinum toxin therapy is safe and effective in treating moderate to severe spasticity. However, the cost of treatment per session is expensive. Therefore, the greatest effect from botulinum toxin injection should be expected whenever possible. The clinicians try to extend the time period between injections for as long as possible in order to reduce the cost. From the results of this study, reduction of spasticity, increased range of joint motion and decreased joint pain may be the most noticeable benefits of the botulinum toxin treatment. With physical therapy program, the patients would more likely benefit from botulinum toxin treatment and probably retain the effects longer than by injection alone. Physical therapy programs aim to improve function by increasing range of motion, selective control, strength, coordination, agility and other components of motor performances(15-17). The physical therapy techniques include patient positioning, muscle stretching, improvement of voluntary control over spastic muscles and strengthening antagonists of spastic muscles. The programs would be changed to maximize the benefit of botulinum toxin injection. The physical therapy program with botulinum toxin injection would extend the time period between repeated injections. The cost can be reduced because of the smaller number of repeated injections.

SUMMARY

This study demonstrates that botulinum toxin therapy is safe and effective in treating chronic upper and lower extremities' spasticity following stroke. The effect of botulinum toxin is lasting for 3 to 6 months. The dosage used in this study is about one-half of the recommended dosage in the literature. The only drawback of this therapy is its high cost (300 US dollars for 100 I.U.).

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การใช้สารพิษชีวภาพโบทุลินัม เอ ในการรักษากล้ามเนื้อหดเกร็งจากโรคหลอดเลือดสมอง: ผลการใช้ในขนาดต่ำ

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วัตถุประสงค์ของการศึกษานี้เพื่อประเมินผลของการใช้ Botulinum A toxin ในการรักษาผู้ป่วยที่มีอาการกล้ามเนื้อหดเกร็งจากโรคหลอดเลือดสมอง โดยได้ทำการศึกษาในผู้ป่วยโรคหลอดเลือดสมองจำนวน 22 ราย ผู้ป่วยทุกรายมีอาการหดเกร็งของกล้ามเนื้อแขนและขาครึ่งซีกที่มีความรุนแรงอยู่ในระดับปานกลางถึงรุนแรง ประสาทแพทย์เป็นผู้ทำการฉีด Botulinum toxin เข้ากล้ามเนื้อทุก 2 เดือน 3 เดือน หรือ 6 เดือน ขึ้นอยู่กับรูปแบบของการหดเกร็งของกล้ามเนื้อ ปริมาณยาที่ใช้ในการฉีดแต่ละครั้งอยู่ระหว่าง 50-100 I.U. นักกายภาพบำบัดจะทำการประเมินผู้ป่วยทั้งแบบ subjective และ objective ก่อนการฉีดยาและหลังการฉีดยาในสัปดาห์ที่ 1, สัปดาห์ที่ 2, และทุก ๆ เดือนหลังการฉีดยาแต่ละครั้ง นักกายภาพบำบัดจะทำการสอบถามเกี่ยวกับความพอใจของการรักษา การประเมินแบบ objective ที่ใช้ในการศึกษานี้คือ Ashworth scale และ Fugl-Meyer Sensorimotor Assessment Form ผู้ป่วยทุกรายมีความพอใจในผลการรักษาด้วยการฉีด Botulinum toxin คือมีการลดลงของการหดเกร็งของกล้ามเนื้ออย่างมากหลังจากการฉีดยา 1-2 สัปดาห์ Botulinum toxin จะมีผลในการลดอาการหดเกร็งของกล้ามเนื้อได้ประมาณ 3-6 เดือน คะแนนที่ประเมินจาก Ashworth scale มีค่าดีขึ้นอยู่ระหว่าง 1-1.5 คะแนน การประเมิน Fugl-Meyer แสดงถึงอาการที่ดีขึ้นอย่างมีนัยสำคัญทางสถิติของการทำงานของแขนและขา และการทรงตัวในผู้ป่วยเกือบทุกราย องศาการเคลื่อนไหวแบบทำให้ในผู้ป่วยทุกรายดีขึ้น และมีอาการปวดที่ข้อลดลง

การศึกษานี้แสดงให้เห็นว่า การรักษาโดยใช้ Botulinum toxin มีความปลอดภัยและมีประสิทธิภาพในการรักษาผู้ป่วยที่มีอาการหดเกร็งของกล้ามเนื้อชนิดเรื้อรังของแขนและขาจากโรคหลอดเลือดสมอง ปริมาณยาที่ใช้ในการศึกษาครั้งนี้มีปริมาณเป็นครึ่งหนึ่งของปริมาณยาที่แนะนำไว้ในการศึกษาที่ผ่านมา ข้อจำกัดประการเดียวที่พบสำหรับการรักษาโดยการฉีด Botulinum toxin คือมีราคาที่สูง (300 เหรียญสหรัฐต่อ 100 I.U.)

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Appendix I: Fugl-Meyer Sensorimotor Assessment Form

Motor Function: Upper extremity
A: Shoulder/Elbow/Forearm
I. Reflex activity:
0: no reflex activity 2: reflex activity elicited
Flexors
Extensors
II. Volitional movement
0: cannot perform 1: can perform partly 2: perform faultlessly
(a) Flexor synergy
Shoulder Retraction
Elevation
Abduction
Outwards rotation
Elbow Flexion
Forearm Supination
(b) Extensor synergy
Shoulder Add-/Inw. Rotation
Elbow Extension
Forearm Pronation
III Mixing the dynamic flexor & extensor synergies
Hand to lumbar spine
Shoulder Flexion 0-90°
Elbow 90° Pro-/Supination
IV. Movements performed with little or no synergy dependence
Shoulder Abduction 0-90°
Flexion 90-180°
Elbow Pro-/Supination
B: Wrist
Elbow 90° Wrist-stability
Elbow 90° Wrist/flexion/extension
Elbow 0° Wrist-stability
Elbow 0° Wrist/flexion/extension
Circumduction
C: Hand
Fingers Massflexion
Fingers Massextension
Grasp a
Grasp b
Grasp c
Grasp d
Grasp e
D: Coordination/speed
Tremor
Dysmetria
Time
Total motor score of the upper extremity (A-D = 64 points)

Motor Function: Lower extremity
E: Hip/Knee/Ankle
I. Reflex activity:
0: no reflex activity 2: reflex activity elicited
Flexors (knee flexor reflex)
Extensors (achillis reflex)
II. Volitional movement
0: cannot perform 1: can perform partly 2: perform faultlessly
(a). Flexor synergy
Hip Flexion
Knee Flexion
Ankle Dorsiflexion
(b). Extensor synergy
Hip Extension

		Adduction
	Knee	Extension
	Ankle	Plantarflexion
III. Sitting position on a chair		
	Knee	Flexion
	Ankle	Dorsiflexion
IV. Standing position		
	Knee	Flexion
	Ankle	Dorsiflexion

F: Coordination/Speed

Tremor
Dysmetria
Time

Total motor score of the lower extremity (E-F = 32 points)

G: Balance

Sit without support
Protective reaction non-affected side
Protective reaction affected side
Stand with support
Stand without support
Stand on non-affected leg
Stand on affected leg

Total score of balance (14 points)

H: Passive joint motion/Joint pain

Passive joint motion

0: only few degrees of range of motion
1: decreased passive range of motion
2: normal passive range of motion

Occurrence of joint pain

0: pronounced pain during all the movement or very marked pain at the end of the actual range of motion
1: some pain
2: no pain

		joint motion	joint pain
Shoulder	Flexion		
	Abduction → 90°		
	Outward rotation		
	Inward rotation		
Elbow	Flexion		
	Extension		
Forearm	Pronation		
	Supination		
Wrist	Flexion		
	Extension		
Fingers	Flexion		
	Extension		
Hip	Flexion		
	Abductuion		
	Outward rotation		
	Inward rotation		
Knee	Flexion		
	Extension		
Ankle	Dorsiflexion		
	Plantarflexion		
Foot	Pronation		
	Supination		
Total score		**joint motion (44 points)**	**joint pain (44 points)**

Appendix II: Muscle Tone Scale (The Modified Ashworth Scale).

0	No increase in muscle tone.
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance through the remainder (less than half) of the range of motion (ROM) when the affected part is moved in flexion or extension.
1+	Slight increase in tone,manifested by catch, followed by minimal resistance throughout the remainder(less than half) of the ROM.
2	More marked increase in muscle tone through most of the ROM, but the affected part is easily moved.
3	Considerable increase in muscle tone, passive movement is difficult.
4	Affected part is rigid in flexion or extension.