Article

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An early botulinum toxin A treatment in subacute stroke patients may prevent a disabling finger flexor stiffness six months later: a randomized controlled trial

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Abstract

Objective: The study asked whether an early botulinum toxin A (BTX-A) injection in subacute stroke patients may prevent a disabling finger flexor stiffness six months later.

Design: Single-blind, randomized pilot study.

Setting: Inpatient rehabilitation centre.

Subjects: Eighteen stroke patients, interval 4–6 weeks, non-functional arm, Fugl-Meyer arm score (0–66) <20, beginning elevated finger flexor tone, randomly allocated to group A or B.

Interventions: In group A patients 150 units BTX-A (Xeomin) injected into the deep and superficial finger (100 units) and wrist flexors (50 units), no injection in group B patients. Comprehensive rehabilitation in both groups.

Main measures: Primary variable was the Modified Ashworth Scale score (0–5) of the finger flexors; secondary variables were whole arm muscle tone with REPAS (a summary rating scale for resistance to passive movement), its motor control with the Fugl-Meyer arm score, and a disability scale, blindly assessed at T0 (start), T1 (four weeks) and T6 (six months).

Results: Homogeneous groups at T0. Significantly less finger flexor stiffness in the BTX-A group at T1 and T6, the mean (SD) Modified Ashworth Scale scores in group A (B) were: 1.7 ± 0.5 (1.6 ± 0.5) at T0; 0.4 ± 0.5 (1.9 ± 0.7) at T1; and 1.4 ± 0.7 (2.4 ± 0.9) at T6. Among the secondary measures, the disability score, namely the items pain and passive nail trimming, was lower in group A at T1 and T6.

Conclusions: The results indicate an effect of early BTX-A injection on finger flexor stiffness six months later, presumably attributable to a reduced contracture development. Effect size calculation suggests inclusion of at least 17 patients per group excluding drop-outs in a warranted placebo-controlled trial.

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Spasticity, prevention, upper limb, stroke, hemiparesis, botulinum toxin

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Introduction

In roughly 30% of the stroke survivors, the arm is severely affected and non-functional. The likelihood of regaining meaningful hand activity six months later is very poor[1] and severe wrist and finger flexor stiffness – disabling hand hygiene, dressing, positioning and eliciting pain – is to be prevented if at all possible. Among a cohort of 211 stroke patients, 40% had developed an elevated muscle tone six months after stroke onset and a severe stiffness, defined as a Modified Ashworth Scale score (0–5) ≥ 3, was observed in 19%. Upper extremity flexor muscle tone started to develop within 2–3 weeks after stroke, and severe distal paresis of the wrist and finger extensors was a predictor.[2–4]

Spasticity is defined as disturbed sensorimotor control presenting as intermittent or sustained involuntary activation of muscles.[5] Concomitant contractures,[6] a pathological condition of soft tissues characterized by stiffness, loss of elasticity and fixed shortenings of the involved tissues, are likely to develop if the abnormal muscle activity holds a joint in either shortened position and/or prevents active movement.[5] The 36-week longitudinal biomechanical study of Malhotra et al. revealed that contractures mainly developed in those stroke patients who did not recover arm function, and they were completely established between 6 and 12 weeks following a stroke, despite the patients receiving routine treatment.[7]

Accordingly, the present pilot study asked whether an early forearm injection of botulinum toxin A (BTX-A) in severely affected patients within 4–6 weeks after stroke could help to prevent a disabling wrist and finger flexor stiffness six months later. By minimizing the spasticity-related abnormal muscle activity holding the joints in a shortened position, the concomitant development of contractures might be prevented. In current clinical practice, BTX-A, which has proved to be effective in numerous randomized controlled trials,[8–12] is normally given once the clinical signs of an elevated muscle tone have become established, therefore it is usually given at least three months after stroke.

Methods

Over a time period of 12 months, 18 eligible patients of an inpatient rehabilitation centre focused on early stroke rehabilitation were recruited (Figure 1, Table 1). They met the following criteria: age <80 years; first time supratentorial stroke; 4–6 weeks after stroke onset; participating in a comprehensive inpatient rehabilitation programme; at least wheelchair-mobilized and partly independent in the basic activities of living with a Barthel Index (0–100) >25;[13] non-functional upper extremity with a Fugl-Meyer motor score (0–66) <20;[14] no (MRC 0) volitional wrist or finger extensor activity;[15] beginning finger and/or wrist flexor stiffness with a Modified Ashworth Scale score (0–5) of 1 or 2, tested while supine by an experienced rater in the morning;[16] no oral antispastic medication prescribed at study onset; no severe neglect syndrome, tested clinically and with the help of a cancellation test; able to give written informed consent, approved by the local ethical committee.

The eligible patients, who had signed the informed consent and had been clinically assessed, were randomly assigned with the help of a computer-generated list to either the experimental or control group. An independent person informed the responsible MD about the group assignment by telephone, the specific treatment of the experimental group was the next day.

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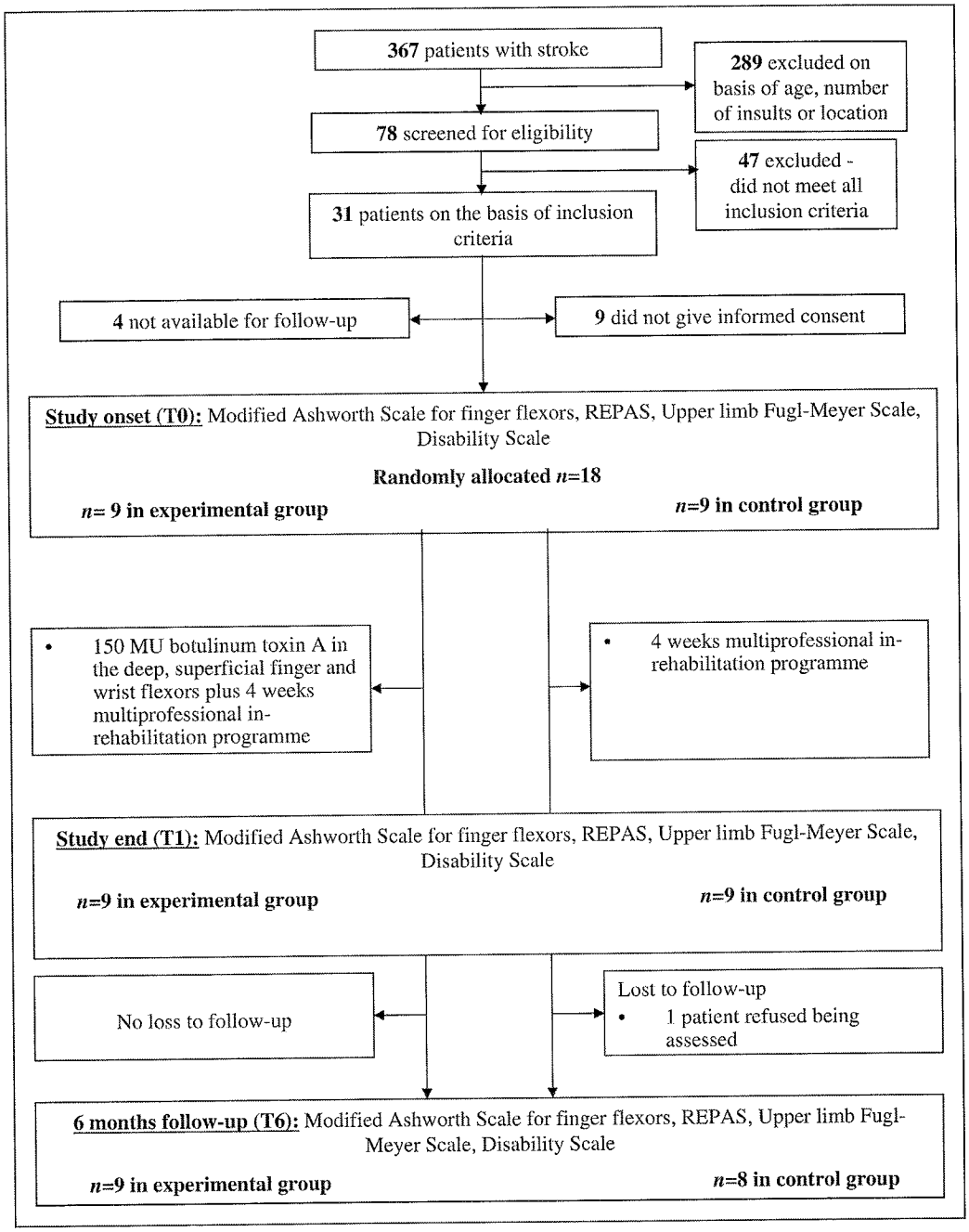

Figure 1. Flowchart of the randomized patients.

In group A patients, an experienced physician injected 150 units BTX-A (Xeomin, 5 mL dilution per vial) ultrasound-guided into the deep and superficial finger flexors (100 units), and the Mm. flexor carpi radialis and ulnaris (50 units), one injection site per muscle. Rapid passive mobilization of the wrist and finger joints for 20–30 minutes immediately followed the injection. This was to promote the internalization of the toxin based on the assumed correlation

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Table 1. Clinical data (means and SD) for both groups at study onset (T0)

	Patients treated with botulinum toxin type A (treatment group)	Patients with no additional botulinum toxin treatment (control group)
n	9	9
Diagnosis		
Ischaemic	6	7
Haemorrhagic	3	2
Hemiparesis		
Left	6	5
Right	3	4
Stroke interval, weeks	5.8 (±1.3)	5.6 (±1.1)
Age, years	57 (±11) [range 37–79]	66 (±11) [range 51–79]*
Sex	F 6; M 3	F 6; M 3
Barthel Index, 0–100	47.1 (±23,9)	45.5 (±22.5)
Patients with neglect syndrome, *n*	0	0
Ambulatory at study onset, *n*	4	4

*Significant difference between groups, $P < 0.05$.

between terminal nerve end activity and toxin uptake.[17] Group B patients received no BTX-A injection. There was no other specific treatment other than the injection.

The multiprofessional motor rehabilitation programme was identical in both groups. It included physiotherapy (45 minutes every workday) and occupational therapy (30 minutes every workday); speech therapy, neuropsychology and spa therapy were administered according to individual needs. An ergometer training was additional. The therapy combined elements of the neurodevelopmental technique and motor relearning programme.

For the arm, tone-inhibiting manoeuvres, gentle passive and assistive mobilizations, facilitation techniques such as holding the extended arm while lying, taking weight over the extended arm, sensory stimulation, bilateral exercises and antispastic positioning were applied in an eclectic manner. A splint, an oral antispastic medication and a BTX-A injection after discharge home were optional. The treating therapists were not actively informed about the BTX-A treatment of the patients of the experimental group, but knowledge on group allocation could not be fully excluded.

An independent person, blind with respect to the group assignment, assessed the patients at three time-points: before the injection (T0), one (T1) and six months (T6) after it. The primary variable was the muscle stiffness of the fingers flexors II–V, assessed with the help of the Modified Ashworth Scale scores (0–5), tested while supine in the morning. The patient was lying on a bench, the elbow was positioned on the bench, the forearm was fully pronated, the rater, sitting beside the patient, supported the wrist held in neutral position with one hand, and passively extended the fingers II–V by applying a constant force on the fingertips with the other hand. Secondary variables were: (a) the whole upper extremity muscle tone, which was assessed with the help of REPAS (0–32)[18] (i.e. the tonus was additionally rated for shoulder abduction, shoulder anteversion, shoulder elevation, elbow flexion, elbow extension, forearm supination, wrist extension and finger extension); (b) motor control, assessed with the help of the Fugl-Meyer motor score (0–66); and (c) the

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stiffness-related disabilities of the fingers and the wrist.

With the help of a questionnaire developed for the study, the patients and their caregivers answered the following six questions:

1. How do you rate the hygiene of your paretic hand, defined as the ease of cleaning the hand?
2. How do you rate the dressing of your paretic upper extremity, defined as the ease of putting on or off a long-sleeved shirt?
3. How do you rate the dressing of your paretic upper extremity, defined as the ease of putting on a glove?
4. How do you rate the pain when the wrist is passively moved?
5. How do you rate the pain when fingers II–V are passively moved?
6. How does the caregiver rate the ease of trimming the nails of the paretic hand?

The patient answered questions 1–3 with the help of 5-point ordinal scale (0–4). Zero indicated that the patient could easily perform the tasks without external help; 1 = mildly disabled, the patient was yet able to carry out the task himself; 2 = moderately disabled, the patient required external help; 3 = severe difficulty, the patient required firm external help; 4 = not possible at all or the caregiver had to apply excessive force. The patients rated questions 4 and 5 with the help of a 5-point ordinal scale (0–4), ranging from 0 (no pain) to 4 (unbearable pain). The caregiver rated question 6 with the help of a 5-point ordinal scale (0–4), with 0 = no problem at all to 4 = impossible to perform. A sum score (0–24) was calculated to derive a disability score.

The prescription of an orthosis, an oral antispastic medication or a BTX-A injection were recorded. Any oral antispastic medication was stopped for three days before T0, T1 and T6.

Homogeneity of the groups before study onset was tested with the help of the Mann–Whitney test. The data were tested for normal distribution with the help of the Kolomogorow Smirnov test. In a next step between-group differences at T1 and T6 were calculated with the help of a Mann–Whitney test ($P \leq 0.025$). In addition, the 95% confidence interval (CI) of paired differences was calculated for the disability sum score to derive the potential clinical relevance.

Results

Seventeen patients (Figure 1) completed the study, one patient of the control group refused assessment at follow-up because the travelling distance was too great. The clinical and demographic data at T0 were comparable, except for an older age in the control group ($P < 0.05$). Side-effects did not occur, except a splint-related skin irritation in the palm of the hand in one control subject.

The Modified Ashworth Scale scores, tested for the finger flexors were significantly lower in the BTX-A group at T1 and T6 (Table 2). Among the secondary variables, the REPAS was significantly lower in the experimental group at T1 ($P = 0.003$), but missed the chosen level of significance ($P = 0.051$) at T6 (Table 2). The Fugl-Meyer scores did not differ between groups at any measurement point (Table 2). The disability sum score (0–24, Tables 3 and 4) was significantly lower in the experimental group at T1 ($P = 0.023$) and T6 ($P = 0.013$). Among the six items, the patients (caregivers) of the experimental group most notably rated the pain (nail trimming) dimensions in favour of the experimental group but not dressing and cleaning the palm of the hand (Table 3).

During the study period, two patients of the experimental and five patients of the conventional group had been prescribed an oral antispastic medication (Baclofen or Tolperison), The odds ratio (OR) for being prescribed oral antispasticity medication during the trial period was 0.2496136 (95% CI 0.01619711 to 2.46286099; $P = 0.3348$) (Table 4). In the control group, one patient had been injected with BTX-A (300 units Botox) for arm flexor spasticity four months after discharge, T6 was postponed for one month and was before the planned next injection. A splint had been prescribed in four (two) patients of the control (experimental) group.

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Table 2. Primary and secondary dependent variables of both groups and *P*-values of between-group differences at study onset (T0), after four weeks (T1) and at six months follow-up (T6)

Variable	Study onset (T0)	*P*-value	After 4 weeks (T1)	*P*-value	At 6 months follow-up (T6)	*P*-value
Modified Ashworth Scale score for finger extension [0–5]						
Treatment	1.7 (±0.5)	0.638	0.4 (±0.5)	0.001*	1.4 (±0.7)	0.025*
	2.0 [1.25–2.0]		0.5 [0.25–1.5]		1.0 [1.0–2.75]	
Control	1.6 (±0.5)		1.9 (±0.7)		2.4 (±0.9)	
	2.0 [1.0–2.09]		2.5 [1.25–3.0]		3.0 [1.5–4.0]	
REPAS [0–32]						
Treatment	9.5 (±3.9)	0.532	2.9 (±3.2)	0.003*	7.7 (±5.6)	0.051
	10.5 [8.25–12.75]		5.5 [2.5–9.5]		8.0 [3.0–13.75]	
Control	8.4 (±3.1)		10.3 (±4.3)		14.0 (±5.9)	
	9.0 [5.0–9.75]		14.0 [7–16.5]		14.5 [6.75–21.0]	
Fugl-Meyer score [0–66]						
Treatment	6.6 (±3.9)	0.654	10.0 (±4.2)	0.788	13.1 (±4.9)	0.857
Control	7.3 (±2.7)		9.9 (±4.2)		12.8 (±5.8)	
Disability Scale [0–24]						
Treatment	9.1 (±3.2)	0.964	5.6 (±2.4)	0.023*	5.7 (±3.2)	0.013*
Control	9.2 (±2.9)		9.0 (±3.2)		10.9 (±4.4)	

*Significant difference between groups, i.e. $P \leq 0.025$.

Table 3. Disability Score (DS) and its single items of both groups and *P*-values of between-group differences at study onset (T0), after four weeks (T1) and at six months follow-up (T6)

Variable	Study onset (T0)	*P*-value	After 4 weeks (T1)	*P*-value	At 6 months follow-up (T6)	*P*-value
Cleanliness of the palm of the hand [DS, 0–4]						
Treatment	1.7 (±0.7)	0.608	1.3 (±0.7)	0.741	1.4 (±0.5)	0.352
Control	1.4 (±1.2)		1.4 (±1.0)		2.1 (±1.6)	
Putting on and off a sleeve [DS, 0–4]						
Treatment	1.3 (±1.0)	0.781	0.8 (±0.7)	0.608	0.9 (±0.6)	0.463
Control	1.4 (±1.0)		1.1 (±1.2)		1.2 (±1.0)	
Putting on a glove [DS,0–4]						
Treatment	1.9 (±0.3)	0.586	1.6 (±0.5)	0.059	1.8 (±0.8)	0.032
Control	2.0 (±0.5)		2.1 (±0.6)		2.9 (±1.1)	
Nail trimming [DS, 0–4]						
Treatment	1.7 (±0.5)	0.609	0.8 (±0.7)	0.004	1.4 (±1.0)	0.018
Control	1.8 (±0.4)		2.0 (±0.7)		2.9 (±1.2)	
Pain during wrist extension [DS, 0–4]						
Treatment	1.4 (±1.2)	0.924	0.6 (±0.7)	0.061	0.9 (±0.8)	0.010
Control	1.4 (±0.9)		1.3 (±0.9)		2.1 (±0.9)	
Pain during finger extension [DS, 0–4]						
Treatment	1.0 (±0.9)	0.888	0.6 (±0.5)	0.088	0.7 (±0.7)	0.007
Control	1.1 (±0.9)		1.0 (±0.5)		1.8 (±0.7)	
Disability Score – total [DS, 0–24]						
Treatment	9.1 (±3.2)	0.964	5.6 (±2.4)	0.023	5.7 (±3.2)	0.013
Control	9.2 (±2.9)		9.0 (±3.2)		10.9 (±4.0)	

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Table 4. 95% Confidence interval (CI) of paired differences (T0 to T1 and T0 to T6) of the sum score of the Disability Score for both groups

Variable	Group	95% CI of paired difference T0 to T1	*P*-value	95% CI of paired difference T0 to T6	*P*-value
Sum score of the Disability Score [0–24]					
	Treatment	2.395 to 4.716	<0.001	2.107 to 4.782	<0.001
	Control	−0.980 to 1.424	0.681	−3.973 to 0.639	0.134

Discussion

An early BTX-A forearm injection in subacute stroke patients with a non-functional arm may prevent a disabling finger stiffness six months later by presumably minimizing the development of contracture. The limitations of the pilot study, notably a small sample size and not placebo-controlled, do not warrant any definite conclusions on the effectiveness at the moment. Effect size calculation suggests inclusion of at least 17 patients per group, excluding drop-outs, in future placebo-controlled trials.

The primary variable, the Modified Ashworth Scale tested for the finger flexors, was significantly lower in the experimental group at T1 and T6. The lower score in the BTX-A group four weeks after injection (T1) was not surprising given the clinically known effect peak of BTX-A on an elevated muscle tone in this time period.

However, the BTX-A injection cannot completely explain the lower finger muscle tone in the experimental group six months later. Its clinical effect duration usually lasts 3–4 months, and in mice new functioning neuromuscular junctions occur within 28 days of intramuscular BTX-A injection.[19] Accordingly, the finger flexor muscle tone in the BTX-A group increased from T1 to T6, even more than in the control group, but this gain started from a lower level.

One may speculate that the neurolytic agent had lessened the spasticity-related intermittent or sustained involuntary muscle activity of the wrist and finger flexors, early occurring after stroke,[5] so that the joints were held in a less fixed position. That again might have delayed and/or diminished the subsequent contracture development resulting in a reduced muscle stiffness at follow-up. In the hereditary spastic mouse, Cosgrove et al. reported that the intramuscular injection of BTX-A prevented the development of contractures.[20]

In highly paretic stroke patients with no volitional wrist and finger extensor activity inducing immobility, it was shown that wrist stiffness started within two weeks after stroke, and concomitant contractures were completely established between 6 and 12 weeks following a stroke.[7] This time-course speaks in favour of an early BTX-A injection, at least in that subgroup of non-functional stroke patients. Later on, with the patients likely to have reached gait ability and competence in the basic activities of living, the therapy may concentrate more on the mobilization of the upper extremity joints in conjunction with tone-inhibiting and facilitating manoeuvres.[21,22]

A lessened muscle tone in the BTX-A group accompanied less disablement, notably with respect to forearm pain and assisted nail trimming dimensions, confirming the results of previous arm BTX-A studies in chronic stroke patients.[10] Active arm and hand functions, assessed with the help of the Fugl-Meyer score, did not differ between the two groups at any time. The low six months Fugl-Meyer score gains, a mean of + 6.5 in the experimental and 5.5 in the control group, rather reflect the known poor prognosis in this subgroup of subjects.[1] On the other hand, Cousins et al. speculated that an early upper limb BTX-A injection in stroke patients with a non-functional upper extremity (defined as those with an initial Action Research Arm Test of 0) might improve

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their functional outcome. However, the authors injected patients within three weeks after stroke onset, the subgroup compromised 17 patients, and the applied Action Research Arm Test has a bottom effect in highly paretic patients, which renders the comparison with the low-functioning patients of the present study difficult.[23]

The limitations of the study are obvious: next to the small number of patients and the missing placebo group, the lack of biomechanical analysis to prove the assumed spasticity and contracture reduction in the BTX-A group, no different dosages, and a potentially longer effect duration of the BTX-A injection on muscle tone should be named.[24] With respect to the recommendable placebo arm in future trials, one has to take into consideration that the intramuscular injection of BTX-A in adult stroke patients with an upper limb flexor spasticity is yet to be registered, so that another placebo-controlled trial would have raised substantial legal barriers in Germany according to the Federal Institute for Drugs and Medical Devices (BfArM).

In summary, an early BTX-A injection of the wrist and finger flexors in severely affected stroke patients within 4–6 weeks after stroke onset may prevent a disabling finger flexor stiffness six months later, which is presumably attributable to reduced contracture development. A placebo-controlled study including different dosage groups is warranted.

Clinical messages

- Early botulinum toxin A injection in severely affected stroke patients might prevent the risk of developing finger flexor stiffness six months later.
- A diminished contracture development presumably explains the effect of the early botulinum toxin A injection.
- A placebo-controlled study with at least 17 patients per group, excluding drop-outs, is warranted.

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