

APPROPRIATE DOSAGE (FROM 100 TO 1000 U) OF INCOBOTULINUMTOXINA IN SPASTICITY

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INTRODUCTION

To perform and optimize spasticity treatment with incobotulinumtoxinA (Xeomin®), an accurate instrumental evaluation of spasticity is needed to identify the best muscles, doses, and times of injection for each patient. The aim of this study was to determine the efficacy and safety of 100 to 1000 units (U) of botulinum toxin type A in the treatment of spasticity according to the individual patient's needs.

METHODS

This observational study lasted 2 years (from March 2016 to March 2018). A group of 120 patients (mean age 64.3±5.23) with spasticity were divided into 3 groups according to the dose used at the beginning of the study. The groupings depended on the severity of spasticity, as evaluated using myometric measurement of tone, an objective means to assess muscle tone in a repeatable and noninvasive way. We obtained a broad view of the pathophysiologic rheologic properties of muscle tissue using MyotonPRO®, a device that provides objective and noninvasive digital palpation of superficial skeletal muscles, at recruitment, at every injection (6 cycles), and during follow-up visits 1 month after each session.

STUDY DESIGN

Patients were initially divided into three groups according to the botulinum toxin A dosage used at the beginning of study (IncobotulinumtoxinA, Xeomin®, Merz Pharma, 100 U/mL in normal saline):

- 1) Group A (30 patients) up to 400 U
- 2) Group B (40 patients) from 400 U to 700 U
- 3) Group C (50 patients) from 700 U to 1000 U

The doses were chosen depending on the severity of spasticity clinically evaluated and on the number of muscles treated.

Treated muscles were Biceps Brachii, Brachioradialis, Triceps Brachii, Superficial Flexorum Digitorum, Ulnar Flexorum Carpi and Opponens pollicis for upper limb, Rectus Femoris, Adductor Magnus, Tibialis Anterior, Flexor Hallucis Longus, Gastrocnemius Medialis and Lateralis, Soleus, Tibialis Posterior and Flexor Digitorum for lower limb, with different average dosage

At screening, examiners selected a target clinical pattern of spasticity to be treated in each injection, patients had to have a muscle tone 2 Ashworth Scale and FIM motor scales score between 26 and 91.

During the study, patients received rehabilitation (stretching of injected muscles, active and passive limb mobilization, walking training and global muscle strengthening) daily for the first 30 days after injection, followed by 3 days a week until next injection.

OUTCOME MEASURES

The evaluation method applied, included the Functional Independence Measure (FIM, an international standard of disability measurement that differentiates motor from cognitive impairment; in the study we have considered only motor impairment) and myometric measurement (MyotonPRO®, tool that determines an objective value of muscle tone, elasticity and stiffness; furthermore, we have taken in consideration (muscle) tone values of superficial muscles).

All assessments for each patient were performed at recruitment (during the 1st injection session), at every infiltrative treatment and during follow ups (made at one month after each session).

STATISTICAL ANALYSIS

Statistical analysis was carried out using the IBM SPSS Statistics program for Windows. Wilcoxon matched-pairs signed ranks test, Wilcoxon rank-sum test (Mann-Whitney U test) and Wilcoxon rank-sum test were used. The alpha level for significance was set at $p < 0.05$. Data are expressed as average

RESULTS

During the observation period, some patients switched to another group because the dosage used increased.

In group A, average doses increased during the study, but there was no statistical significance. At the third infiltration, we increased dosage in 10 patients (33%) due to poor clinical effects or to treat more muscles, so they switched in group B. In the following injections, these patients improved their clinical and instrumental measurement of spasticity (figure 1 and 2).

In group B, average doses increase was not statistically significant during the study. After the first infiltration, 8 patients (20%) showed no clinical and instrumental improvement, so we increased dosage (we treated muscles with greater dosage rather than treated more muscles) and they switched in group C. In the following injections, these 8 patients improved their clinical and instrumental measurement of spasticity (figure 3 and 4).

In the group C, average doses at the end of study was statistically significant compared to the beginning (from 775,65±30,45 to 986,65±13,67, $p < 0,05$) (figure 5). During the study all patients improved their clinical and instrumental measurement of spasticity

DISCUSSION

This study demonstrated long term treatment efficacy of IncobotulinumtoxinA in the management of muscle spasticity using variable doses.

According to severity of spasticity, clinically and instrumental evaluated, and to number of muscles treated, we inoculated different botulinum toxin A doses verifying spasticity improvement after each injection cycle. In 10 of 30 patients in group A and 8 of 40 patients in group B, we increased administered dose after the third and first infiltration respectively due to a non significant clinical and instrumental efficacy; in group A patients, we increased units for each muscle or we increased number of muscles treated, in group B patients, we increased units for each muscle treated. Different study demonstrated that improper injection technique or the denatured toxin result into therapeutic failure. In this eighteen patients, injection technique or toxin A reconstitution were the same as the other patients, so therapeutic failure was due to incorrect doses or clinical evaluation of the patient. After total units administered change, spasticity improved after each injection effectuated during the study in these eighteen patients.

The ease of dosage changing and the use of higher doses than approved, is possible according to the ratio known as Therapeutic Index (TI) or Therapeutic Ratio (TR). In clinical practice, the TI is the range of doses at which a medication appeared to be effective in clinical trials for a median of participants without unacceptable adverse effects. For most drugs, this range is wide enough, and the maximum concentration of the drug and the area under the concentration-time curve achieved when the recommended doses of a drug are prescribed lie sufficiently above the minimum therapeutic concentration and sufficiently below the toxic concentration. Thus, it can be expected that at the recommended prescribed doses, drugs present clinical efficacy with an adequate safety margin. Larger TI means safer drug. It is generally considered that a drug has a good safety profile if its TI exceeds the value of 10. Patients with multifocal spasticity benefits from botulinum toxin A treatment with higher total doses because different study demonstrated high TI of IncobotulinumtoxinA. With escalating total doses, a higher number of spasticity patterns was successfully treated, leading to increasing improvements in muscle tone, indicated by consistent decreases in clinical and instrumental evaluation. In this study, the use of doses from 100 to 1000 UI demonstrate that the IncobotulinumtoxinA has a wide therapeutic window, indicating drug safety use since even at high doses, side effects was poorly significant and transient.

CONCLUSION: Using the larger therapeutic index and therapeutic window of incobotulinumtoxinA, we applied an appropriate dose individualized according to multidisciplinary programs for each patient rather than a standard- or high-dose treatment.

KEYWORDS: Appropriate treatment; Botulinum toxin type A; Spasticity; Therapeutic index

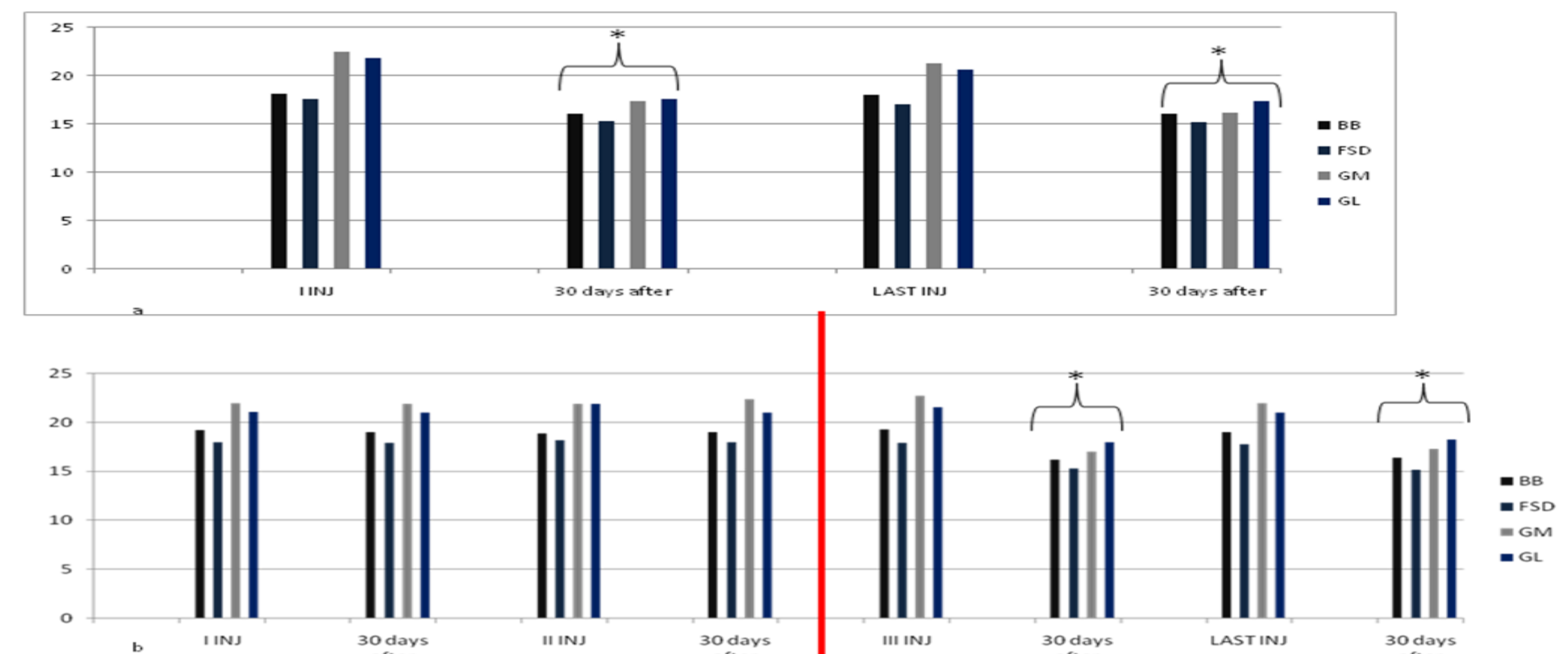


Fig.1: myometric muscles tone evaluation in the group A. This figure shows statistically decrement of muscles tone after 30 days of first and last injection in 20 patients treated with dosage up to 400UI (a). For 10 patients of this group, muscles tone reduction was lower in the first and second cycle of injection; when we increase dosage (up to 700UI, red line) due to increase units for each muscle or to inject other muscles not evaluated with myotonPRO®, reduction was statistically after 30 days for each cycle of injection (b). * $p < 0,05$

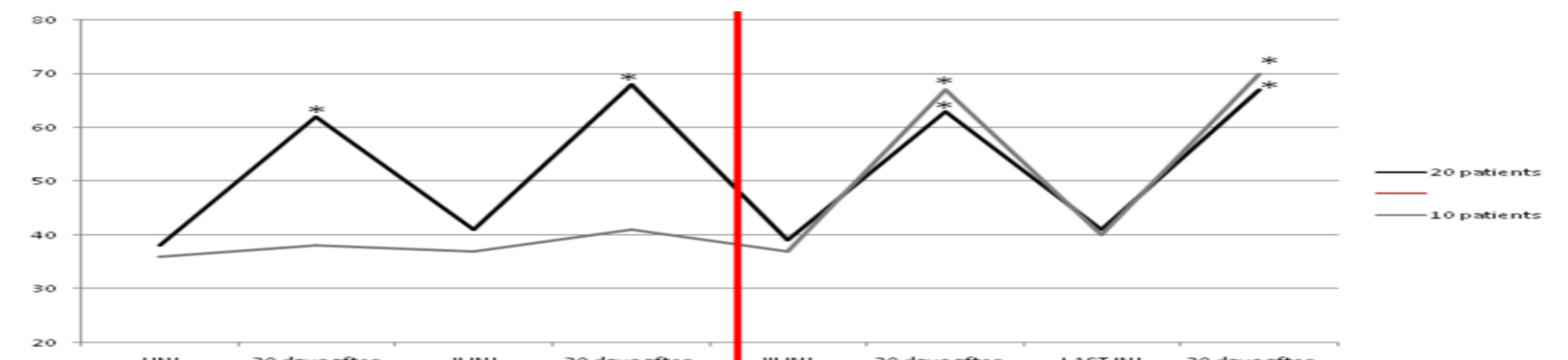


Fig.2: FIM value in group A. Black line shows statistical improvement of FIM in 20 patients treated with dosage up to 400UI. Instead, the grey line shows a statistical improvement of FIM in other 10 patients of this group when we increase dosage (up to 700UI, red line) due to increase units for each muscle or to inject other muscles. * $p < 0,05$

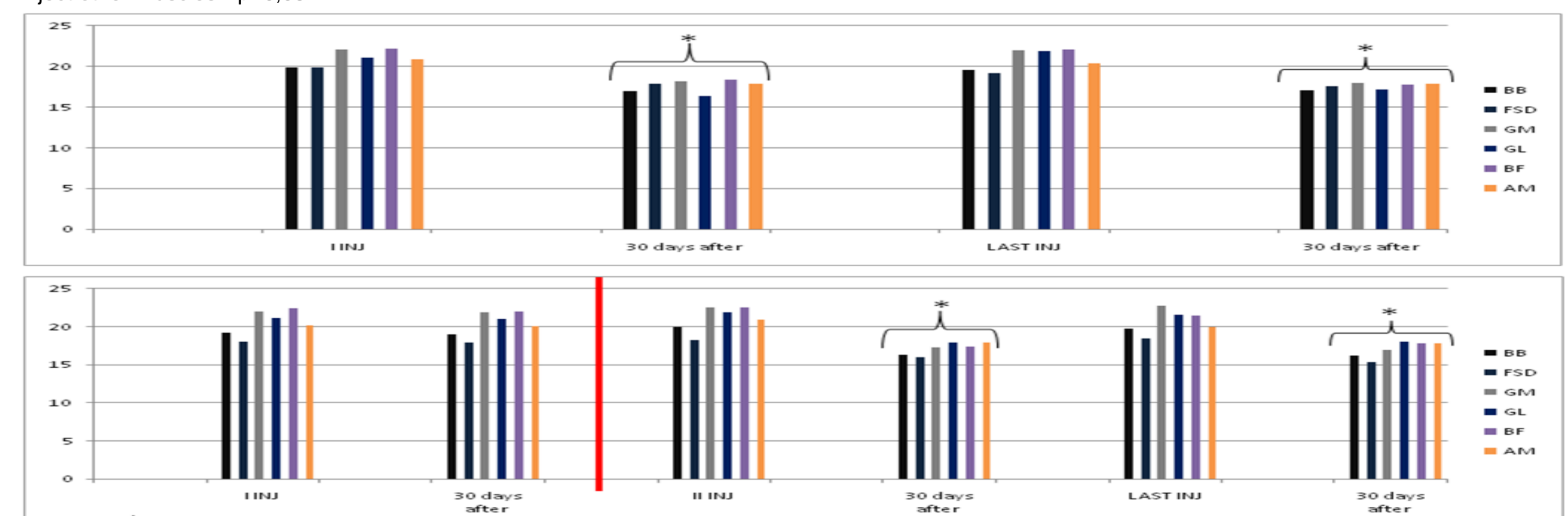


Fig.3: myometric muscles tone evaluation in the group B. This figure shows statistically decrement of muscles tone after 30 days of first and last injection in 32 patients treated with dosage from 400UI to 700UI (a). For 8 patients of this group, muscles tone reduction was lower in the first cycle of injection; when we increase dosage (up to 1000UI, red line) due to increase units for each muscle (rather than injected other muscles), reduction was statistically after 30 days for each cycle of injection (b). * $p < 0,05$

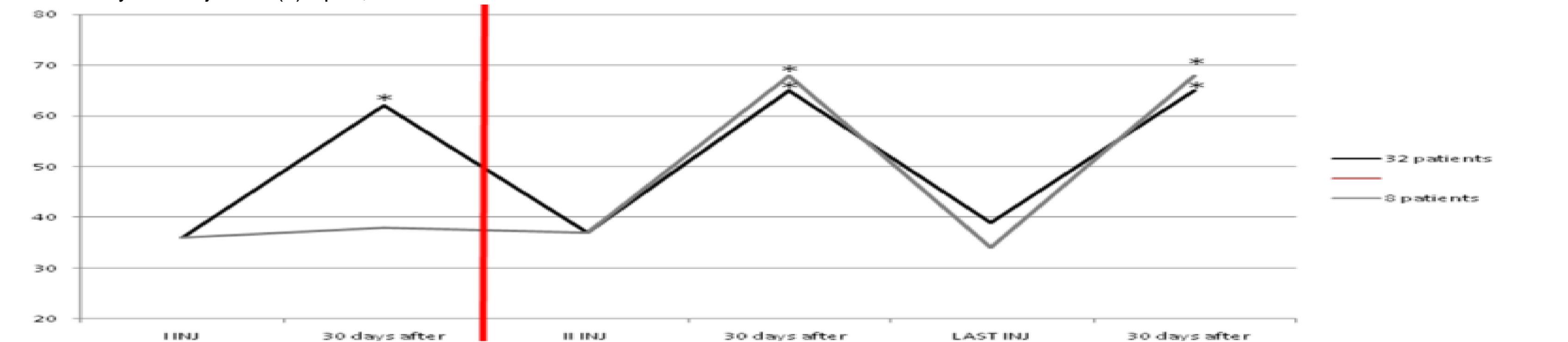


Fig. 4: FIM value in group B. Black line shows statistical improvement of FIM in 32 patients treated with dosage up to 700UI. Instead, grey line demonstrates statistically improvement of FIM in other 8 patients of this group when we increase dosage (up to 1000UI, red line) due to increase units for each muscle. * $p < 0,05$

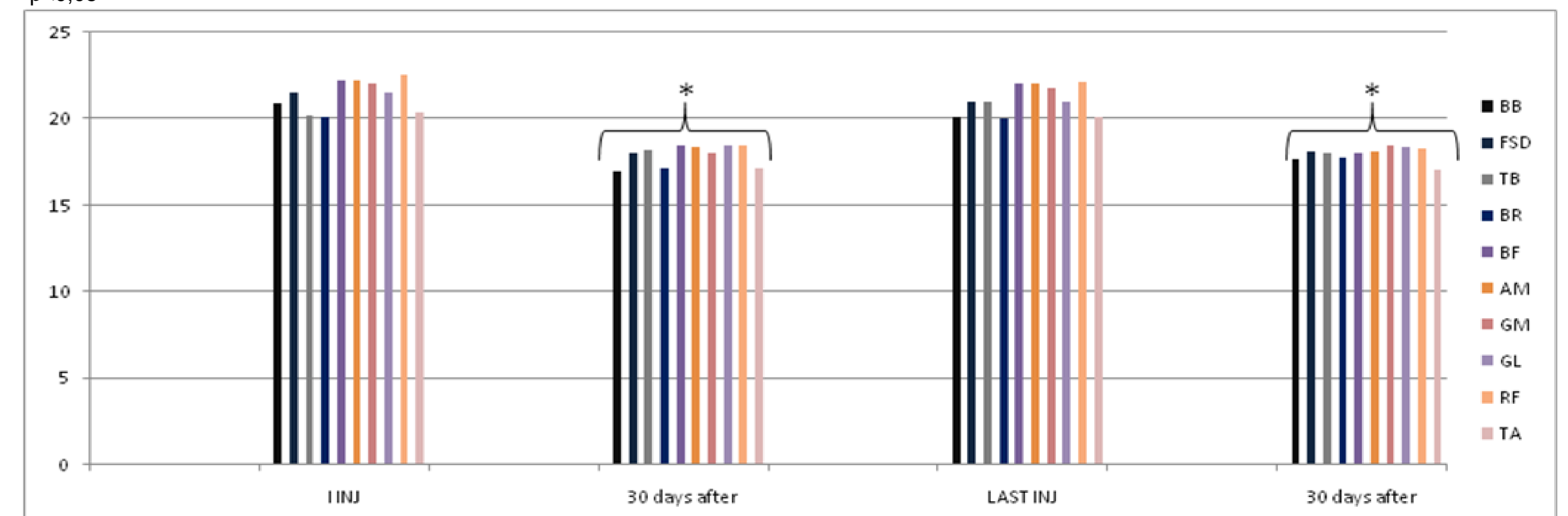


Fig.5: myometric muscles tone evaluation in the group C. In each cycle of treatment, statistically decrement of muscles tone after 30 days of injection was found; this figure shows data of first and last cycle of treatment. * $p < 0,05$

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