Research article

New methodological aspects in rehabilitation after proximal humerus fracture

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Abstract: Proximal humerus fracture ranks third in the elderly after femoral neck fractures and distal radius fractures, and seventh in adults, and the risk of occurrence is related to advancing age. In this study we aimed to analyze the efficacy of a 24-weeks physical therapy programme based on a particular methodology consisting of the reprogramming of the specific proprioceptive neuromuscular facilitation techniques added to the classical physical therapy and by introducing modern interactive therapies and technologies: Capacitive Resistive Electric Transference, Instrument Assisted Soft Tissue Mobilization, kinesiological tapes and PRAMA system, compared with classical physical therapy. Our study included 26 patients, aged between 18 and 55 years, with proximal humerus fracture, who complete the 24-weeks rehabilitation programme. We assessed pain, shoulder range of motion, muscle strength and the ability to perform activities of daily living. The statistical analysis was performed using IBM SPSS and Excel 2021. The results showed statistically significant improvement in all shoulder motion, increased muscle strength, decreased pain, and a better ability to perform daily activities. The physical therapy programme based on the proposed particular methodology has proven to be more effective than classical physical therapy, both regarding the improvement of the movement parameters compared to the physiological values, as well as the symmetry of both shoulders.

Keywords: proximal humerus fracture; rehabilitation; range of motion; muscle strength; pain; activities of daily living

1. Introduction

Fractures of the proximal end of the humerus have an incidence directly proportional to the advancing in age. In terms of frequency in the elderly population, this type of fracture ranks third after the femoral neck fractures and the fractures of the distal end...
of the radius, and seventh in the adult population [1]. Both because of their high frequency, with an incidence ranging from 4% to 10% of all fractures [2], and because of their immediate and late complications, fractures of the proximal end of the humerus are the subject of a large number of studies related to their etiopathogenic mechanisms, to the surgical and additional methods of their treatment, and to the physical therapy interventions in the recovery therefrom. Road traffic accidents, work accidents, sports injuries and physical assaults between domestic partners and collective conflictual violence are the main causes of these fractures among active people. According to most of the studies the highest frequency is reported among males [3–5]. Studies also showed a bimodal distribution of these fractures, depending on the mechanism of energy discharge. The bimodal criteria are based on the age of the patient. High-energy discharge fractures are characteristic of patients under 55 years of age, active people more engaged in driving motor vehicles and engines, exposed to physically demanding activities whether occupational or non-occupational, who play contact sports, as well as exposed to blows or other forms of intimate partner violence or collective conflict. On the other hand, there are numerous studies that approach the etiopathogenesis of this type of fracture at patient vulnerable due to age, characterized by low bone density and factors associated thereto, history of bone lesion, sedentarism and abnormal body mass index (IMC), cardiovascular, neurological and psychological comorbidities [6]. The four known severe complications of the proximal humeral extremity fractures are the lack of consolidation, vascular necrosis of the humeral head, rigidity and disfunction of the rotator cuff muscles which have strong negative effects on the functional results. These are the main challenges that hinder the recovery of the functional capacity before the traumatic event [7]. By the significant disabilities they induce, these fractures require a special approach strategy in selecting the type of treatment and in directing the functional recovery [8,9]. The specialized strategy confirms good, stable results of the conservative treatment of the proximal humeral extremity fractures, with minimum displacement or with two fragments (Neer 1 and Neer 2) [10]. Unlike the two-fragment fractures, there are numerous controversies regarding the conservative treatment versus the surgical one in the fractures with three or four segments (Neer 3, Neer 4). The development of the technical surgical treatment possibilities (various types of osteosynthesis, hemiarthroplasty and the total reverse polarity shoulder arthroplasty) turned them into the standard option [11–14]. The collaboration of the interdisciplinary team (physical medicine and rehabilitation physician, physical therapist, psychologist, occupational therapist, nurse) is essential in the design and development of a quality prognostic, i.e., to assess the efficiency of the key aspects in the rehabilitation of patients with orthopedically or surgically treated proximal humerus fractures [15–17].

The purpose of the study was to analyze the efficacy of a physical therapy programme based on a particular methodology consisting of the reprogramming of the specific proprioceptive neuromuscular facilitation techniques added to the classical physical therapy and by introducing modern interactive therapies and technologies: Capacitive Resistive Electric Transference (TECAR), Instrument Assisted Soft Tissue Mobilization (IASTM), kinesiological tapes and PRAMA system.

TECAR therapy is a non-invasive, endogenous therapy that uses electrical currents, induced by a capacitive/resistive monopolar radiofrequency (0.45-0.6 MHz), to generate deep tissue heating [18,19]. The device consists of two electrodes, one positive and one negative, connected to a generator that creates a potential difference, one electrode being positioned at a fixed point near the area to be treated and the other one applied as a light pressure massage by the physiotherapist [20]. The device can be used in capacitive mode, which has surface effects on tissues with a significant water content, such as muscle tissue or the lymphatic system, and resistive mode, which has effects on tissues with a low water content, such as bone tissue, tendons and ligaments [20]. The therapeutic effects of TECAR are vasodilatation, increase of local cellular metabolism, and improvement of microcirculation [18]. An important advantage of TECAR therapy is the fact that it does not interfere with other therapeutic methods, being a good complementary method in the case of elderly patients [20].
The IASTM therapy is a non-invasive therapy, based on the assisted mobilization of soft tissues with the help of specialized instruments, which gives the physical therapists the opportunity to effectively locate myofascial dysfunctions, such as: fibrosis, fascial adhesions, inflammation, trigger points [21,22]. IASTM therapy in fractures of the proximal extremity of the humerus helps to increase the mobility of the scapulo-humeral joint by restoring the flexibility of the shoulder muscles, due to the improve-ment of fibroblast proliferation and local vascularization, the remodeling of the collagen fiber matrix and the reduction of tissue damage and adhesions [22,23].

Physical therapy is the primary method of rehabilitation for the shoulder and upper limb following fractures of the proximal extremity of the humerus treated ortho-pedically or surgically, and includes primarily segmental exercises to increase shoulder and upper limb mobility, toning exercises of the shoulder and upper limb muscles, growth exercises of the stability of the shoulder joint, and upper limb postural control. However, physical therapy is often based on the recovery of general motor character-istics rather than the specific daily and professional activities required for active pa-tients. As a result, it is vital to focus exercises on specific tasks in order to recover spe-cific movements employed during professional and recreational activities, as well as early independence in conducting daily physical activities [24].

Kinesiology tape have proven effective in reducing pain, improving muscle func-tion by improving tone, supporting joints, stimulating proprioception, manipulating joints, increasing stability, normalizing blood circulation, and stimulating lymphatic drainage [25–27].

PRAMA system uses a combination of music, lighting, and sychronization in an interactive room with lights, LED sensors, interactive floors, different functional markings and various software in order to help patient to improve his movement skills.

This strategy was implemented in patients with fractures of the upper humerus extremity, which, due to impaired joint physiology, affected their performance in daily, professional (creative) and recreational activity.

The objective of the study was to establish the effectiveness of specific propriocep-tive neuromuscular facilitation techniques, TECAR and IASTM therapies, kinesiologi-cal tapes and modern PRAMA interactive technology, named “physical therapy”, by moni-toring the evolution of ROM, muscle strength, pain, and the ability to perform daily living activities, during rehabilitation treatment, compared to classical physical therapy.

2. Results

The study group consisted of 22 men (84.6%) and 4 women (15.4%). The mean age of patients was 40.92 (±9.033) years, with a minimum of 18 and a maximum of 55 years.

In 80.8% of the cases, the affected limb was the dominant one.

The fractures were mostly provoked by road accidents (53.9%), while 15.4% were caused by sports trauma. To a lesser extent, the fractures were caused by falls from height – labor accidents (11.5%), collective conflictual violence (11.5%) and intimate partner violence (7.7%), as shown in Figure 1.
Figure 1. Distribution of fractures according to etiology

The fractures with no displacement represented the highest percentage (61.6%). The non-displacement fractures were treated orthopedically - Dessault bandage (61.6%). The fractures with displacements were treated surgically through two methods, i.e., by osteosynthesis with plate and screws (26.9% of the total) and by osteosynthesis with locked intramedullary nailing (11.5%).

Proximal humeral pain

Proximal humeral pain was assessed using Visual Analog Scale for Pain (VAS scale) [28]. By analyzing proximal humeral pain, we observed that during the initial testing, the average value of the scores was 8.08 (±0.935), with a minimum score of 6 and a maximum score of 10. At the final testing (after 24 weeks), the average value of the scores was of 1.38 (±1.551), with a minimum score of 0 and a maximum score of 5. In order to test the difference obtained during the initial and final test-interviews of the variable “proximal humeral pain” we used the t-test on paired samples, as shown in Table 1.

Table 1. Proximal humeral pain evolution after physical therapy programme

<table>
<thead>
<tr>
<th>Testing Initial - Final (I-F)</th>
<th>Paired Differences</th>
<th>95% Confidence Interval of the Difference</th>
<th>t</th>
<th>df</th>
<th>Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Std. Deviation</td>
<td>Mean</td>
<td>Std. Error</td>
<td>Lower</td>
</tr>
<tr>
<td>Pain I-F</td>
<td>6.692</td>
<td>1.320</td>
<td>0.259</td>
<td>6.159</td>
<td>25.858</td>
</tr>
</tbody>
</table>

The t-test proves that the difference between the test results was statistically significant (p<0.001), thus resulting a significant statistical decrease in shoulder pain after the applied physical therapy programme.

Shoulder range of motion

Mobility in the sagittal plane (flexion and extension movements)

The average value of ROM for shoulder flexion at the initial testing was of 49.65° (±23.55), with a minimum of 20° and a maximum of 90°. At the final testing, the average value was of 165.69° (±21.058), with a minimum of 125° and a maximum of 180° (Figure 2).

Figure 2. Initial and final shoulder flexion

The average value of ROM for shoulder extension at the initial testing was of 15.23° (±5.708), with a minimum of 5° and a maximum of 28°. At the final testing, the average
value was of 44.88° (±5.362), with a minimum of 35° and a maximum of 50° (Figure 3).

**Figure 3.** Initial and final shoulder extension

**Mobility in frontal plane (abduction and adduction movements)**

The average value of ROM for shoulder abduction at the initial testing was 38.58° (±17.411), with a minimum of 5° and a maximum of 65°. At the final testing, the average value was 157.00° (±28.591), with a minimum of 106° and a maximum of 180°.

The average value of ROM for shoulder adduction at the initial testing was 11.58° (±6.658), with a minimum of 0° and a maximum of 25°. At the final testing, the average value was 33.27° (±4.295), with a minimum of 23° and a maximum of 38°.

**Mobility in transversal plane (internal and external rotation movements)**

The average value of ROM for shoulder internal rotation at the initial testing was 19.96° (±13.707), with a minimum of 0° and a maximum of 53°. At the final testing, the average value was 81.46° (±14.275), with a minimum of 45° and a maximum of 95°.

The average value of ROM for shoulder external rotation at the initial testing was 19.69° (±13.236), with a minimum of 0° and a maximum of 53°. At the final testing, the average value was 78.15° (±13.284), with a minimum of 40° and a maximum of 90°.

The evolution of all shoulder motion ranges after physical therapy programme is shown in Table 2.

**Table 2. Evolution of shoulder motion ranges after physical therapy programme**

<table>
<thead>
<tr>
<th>Testing Initial - Final (I-F)</th>
<th>Paired Differences</th>
<th>t</th>
<th>df</th>
<th>Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Std. Deviation</td>
<td>Std. Error Mean</td>
<td>95% Confidence Interval of the Difference</td>
</tr>
<tr>
<td>Flexion I-F</td>
<td>-116.038</td>
<td>27.788</td>
<td>5.450</td>
<td>Mean</td>
</tr>
<tr>
<td>Extension I-F</td>
<td>-29.654</td>
<td>5.520</td>
<td>1.083</td>
<td>Mean</td>
</tr>
<tr>
<td>Abduction I-F</td>
<td>-118.423</td>
<td>23.322</td>
<td>4.574</td>
<td>Mean</td>
</tr>
<tr>
<td>Adduction I-F</td>
<td>-21.692</td>
<td>5.424</td>
<td>1.064</td>
<td>Mean</td>
</tr>
<tr>
<td>Internal rotation I-F</td>
<td>-61.500</td>
<td>16.061</td>
<td>3.150</td>
<td>Mean</td>
</tr>
<tr>
<td>External rotation I-F</td>
<td>-58.462</td>
<td>15.190</td>
<td>2.979</td>
<td>Mean</td>
</tr>
</tbody>
</table>

Outcome measure after physical therapy programme relative to the values of the unaffected shoulder, reported as difference in the range of motion (ROM) between the two shoulders, is shown in Table 3.
Table 3. Outcome measure after physical therapy programme expressed as the difference in ROM between the two shoulders

<table>
<thead>
<tr>
<th>Shoulder movement</th>
<th>Initial testing</th>
<th>Final testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexion</td>
<td>120.35°</td>
<td>4.31°</td>
</tr>
<tr>
<td>Extension</td>
<td>39.77°</td>
<td>10.12°</td>
</tr>
<tr>
<td>Abduction</td>
<td>136.42°</td>
<td>18°</td>
</tr>
<tr>
<td>External rotation</td>
<td>70.31°</td>
<td>11.85°</td>
</tr>
</tbody>
</table>

Muscle strength

Muscle strength testing was performed using Manual Muscle Testing scale [29,30]. The average score of muscle strength at the initial testing was 1.54 (±0.508), with a minimum score of 1 and a maximum score of 2+. At the final testing the average value of the scores was 4.85 (±0.368), with a minimum score of 4- and a maximum score of 5. The evolution of muscle strength after physical therapy programme is shown in Table 4.

Table 4. Evolution of muscle strength after physical therapy programme

<table>
<thead>
<tr>
<th>Testing Initial - Final (I-F)</th>
<th>Paired Differences</th>
<th>95% Confidence Interval of the Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Std. Deviation</td>
</tr>
<tr>
<td>Muscle strength I-F</td>
<td>-3.308</td>
<td>0.471</td>
</tr>
</tbody>
</table>

Independence in performing activities of daily living

Assessment of the independence in performing daily, professional, and recreational activities was performed using a 3-point ordinal scale (0-dependent, 1-partially dependent, 2-independent). The higher the score, the more independent the patient is in performing the task. At the initial testing, the average value of the scores was 0.31 (±0.471), with a minimum score of 0 and a maximum score of 1, and, at the final testing the average value of the scores was 1.92 (±0.272), with a minimum score of 1 and a maximum score of 2. The evolution of independence in performing ADLs after physical therapy programme is shown in Table 5.

Table 5. Evolution of independence in performing ADLs after physical therapy programme

<table>
<thead>
<tr>
<th>Testing Initial - Final (I-F)</th>
<th>Paired Differences</th>
<th>95% Confidence Interval of the Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Std. Deviation</td>
</tr>
<tr>
<td>Independence in ADLs I-F</td>
<td>-1.615</td>
<td>0.496</td>
</tr>
</tbody>
</table>

3. Discussion

The study group included 22 men and 4 women, aged between 18 and 55 years, with an average age of 40.92 (±9.033) years.

In relation to trauma ethology, the group consisted of fractures caused by: road accidents (53.9%), sports trauma (15.4%), labor accidents (11.5%), collective conflictual violence (11.5%) and intimate partner violence (7.7%).

It was analyzed the ratio of injured limb to dominant limb to highlight the functional and psychological impact that the traumatic event had on these patients. The event can
generate complications with a complete spectrum of somato-psychic-affective severity. These complications, which can be highlighted with this report, can, in turn, generate through positive feedback other locomotor difficulties in the kinematic chain where the primary injury involved the humeral fracture. The difficulties can lead to further impairments in performing physical and professional activities, either directly or mediated by the psychosomatic co-affect. The results shown that in 80.8% of the cases, the injured limb was the dominant one.

The outcome measures after the rehabilitation program indicated higher values of ROM than values obtained after the classical physical therapy program, both in terms of active ROM, and as difference between the two shoulders. Thus, after 24 weeks of therapy, our patients achieved the following average values of ROM shoulder movements:

- flexion 165.69°, which corresponds to a difference of 4.31° between the two shoulders, compared to classical physical therapy, 128° [31] and, respectively 10.6° [32] between the two shoulders
- abduction 157.00°, which corresponds to a difference of 18° between the two shoulders, compared to classical physical therapy, 117° [31] and, respectively 10.5° [32] between the two shoulders
- external rotation 78.15°, which corresponds to a difference of 11.85° between the two shoulders, compared to classical physical therapy, 44° [31] and, respectively 11.7° [32] between the two shoulders

The results indicate a decrease in shoulder pain after the applied physical therapy programme, from 8.08 to 1.38 on Visual Analog Scale for Pain.

The t-test on paired samples (Table 3) showed that the difference between tests was statistically significant (p<0.001), indicating a significant increase in all shoulder motion ranges after physical therapy: flexion, extension, abduction, adduction, internal and external rotation.

Evolution of muscle strength after physical therapy programme (Table 5) showed the statistically significant increment of the shoulder muscle strength after the physical therapy programme applied.

The evolution of independence in performing ADLs after physical therapy programme (Table 6) showed the significant statistic increment of the patients’ independence in performing daily tasks, of the professional and recreational type, further to the physical therapy programme applied.

4. Materials and Methods

The study group consisted of patients from various private medical rehabilitation clinics that met the selection criteria. After the application of the inclusion and exclusion criteria, out of a total of 59 patients with fractures of the proximal extremity of the humerus treated either orthopedically or surgically, by various types of osteosynthesis, with the purpose of recovering the functionality of the shoulder joint, 26 patients were selected. The inclusion criteria were: patients’ informed agreement and consent; patients aged between 18 and 55 years; economically and professionally active patients; patients in a normal somatopsychic state. The exclusion criteria were: lack of the patients’ informed agreement and consent; patients younger than 18 years; patients over 55 years; polytraumatized patients who had to undergo (at the same time) various recovery programmes for several injuries; patients with cardiovascular conditions, with neuropsychological diseases, congenital diseases, metabolic diseases (diabetes, dyslipidemia, obesity), endocrine diseases; patients with recent epidemiological conditions; bone fracture pathologies (osteopenia, osteoporosis). The low caseload is due to the triage, which avoided specialties such as: traumatology, emergency medicine, orthopedic surgery, plastic surgery, or radiology.

To re-establish functional independence, the selection and progress of the techniques and methods were adjusted to the patients’ individual abilities and needs. Regardless of the applied treatment method, the physical therapy mainly included segmented exercises to increase the mobility of the shoulder girdle, of the shoulder and of the free upper limb,
exercises to tone the muscles of the shoulder girdle, of the shoulder and upper limb, exercises to increase the stability of the shoulder joint. Other objectives included the training of the postural control of the upper limb and the recovery of the general motor characteristics. These were implemented by targeting the exercises to various tasks and demands. Equally important was the follow-up of the recovery of the precocious independence in the performance of the movements specific to daily life and of those useful in the performance of professional and recreational activities [33,34]. The physical therapy rehabilitation strategy was implemented depending on the stages of the healing and recovery processes, as shown in Table 6.

Table 6. The objectives of the rehabilitation plan for each stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Period</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Weeks 0-4</td>
<td>• Teach the patient how to protect the humerus</td>
</tr>
<tr>
<td>Early recovery stage</td>
<td></td>
<td>• Independence in transfers and ADLs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Relief of pain and inflammation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Gradual recovery of mobility, reaching 90° passive shoulder flexion in the first 2 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Complete recovery of passive flexion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Recovery of internal and external rotation and abduction of the shoulder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Initiation of active mobilizations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pain and inflammation management</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Recovery of dynamic stability of the shoulder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Recovery of mobility at the level of the shoulder blade</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Weeks 4-6</td>
<td>• Maintaining full flexion ROM</td>
</tr>
<tr>
<td>The actual recovery stage</td>
<td></td>
<td>• Recovery of active flexion up to 120°</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Gradual recovery of muscle strength and endurance in the shoulder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Optimization of neuromuscular control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Gradual return to ADLs and IADLs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Maintaining full active pain-free range of motion in all planes</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Weeks 6-12</td>
<td>• Gradual reintegretion into sports activities (recreational or competitive)</td>
</tr>
<tr>
<td>The late recovery stage</td>
<td></td>
<td>• Development of muscle strength and endurance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Progression for closed kinetic chain exercises</td>
</tr>
</tbody>
</table>

According to the adopted strategy, the precocious recovery stage was aimed at the improvement of the symptomatology (pain, dread, functional impotence), the modulation of the inflammatory process and of the signs thereof (oedema, swelling, functional impotence) and muscle toning at shoulder level. Since the scapulohumeral joint was the anatomical-physiologically injured and strengthened area, the recovery of its mobility started by graded exercises depending on the post-therapy status. The actual recovery stage included the full restoration of the shoulder’s motion range on all planes and the restoration of the muscle force and strength. The final rehabilitation stage envisaged the recovery of the general and special properties of the muscles, as well as of the force and strength parameters. The final stage implicitly envisaged the optimization of the neuromuscular control, with the return to the daily and professional activities and with the reintegration into the sports activities (recreational or competitive). The kinetic techniques applied in the recovery of the shoulder after fractures of the proximal extremity of the humerus were: static kinetic techniques – isometric contractions; dynamic kinetic techniques – passive and passive-active mobilizations of the shoulder joint on all planes, active mobilizations.
in open and in closed kinetic chain; local relaxation techniques of the shoulder muscles – Codman pendulations.

The originality of the physical therapy strategy consisted in the introduction in the exercise program of specific neuromuscular facilitation techniques (Rhythmic Initiation - RI, Relaxation - Opposition - RO, Rhythmic Stabilization - RS) and modern therapies and technologies (TECAR - for producing vasodilation, increasing local cellular metabolism, improving microcirculation; IASTM - for increasing joint mobility by restoring flexibility to the shoulder muscles, due to improved fibroblast proliferation, improved local vascularization, remodeling of collagen fiber matrix and reduction of tissue damage and adhesions; kinesiology tapes - for pain reduction, improvement of muscle function, joint support function, stimulation of proprioception, joint manipulation and direction of movement, increased stability, normalization of blood circulation and stimulation of lymphatic drainage and PRAMA interactive system - for improving fitness, balance maintenance, coordination, agility and reaction time through customized programs from hundreds of exercises in the online platform).

Statistical analysis was performed using IBM SPSS Statistics version 26 and Excel 2021.

5. Conclusions

The specific proprioceptive neuromuscular facilitation techniques, TECAR and IASTM therapies, kinesiological tapes and modern PRAMA interactive technology in rehabilitation after proximal humerus fracture showed a greater improvement in the evolution of ROM, muscle strength, pain, and the ability to perform daily living activities, compared to classical physical therapy programme.


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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Research Ethics Committee of University of Medicine and Pharmacy “Carol Davila” (protocol code 9914/04.04.2023).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: The study’s data can be obtained upon request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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