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“VICTOR BABEȘ” TIMIȘOARA**

DEPARTMENT XV – ORTHOPAEDICS AND TRAUMATOLOGY

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DOCTORAL THESIS SUMMARY

**OSTEOSYNTHESIS IN DIAPHYSEAL FRACTURES OF THE HUMERUS,
FEMUR, AND TIBIA**

EXPERIMENTAL AND CLINICAL STUDY

SCIENTIFIC COORDINATOR

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Keywords: osteosynthesis, femur, tibia, humerus, intramedullary nail, plate, bone healing.

INTRODUCTION

In our days, orthopaedic surgeons are trained to consider fractures like a multifaced pathology and not only a strictly bone related illness. All the systemic effects must be taken into consideration, such as immunologic, pulmonary, gastro-intestinal and neurologic response, so that the correct timing and type of treatment is applied, for each patient in case.

The surgical treatment of diaphyseal fractures of the long bones is in a continuous evolution, based on the newest research into bone healing, the role of the surrounding tissue, new types of reduction and fixation techniques have been introduced.

Even so, faced with a multitude of therapeutic choices, the decision-making process has become much more complex, making room for more research into the matter.

The surgical treatment of long bones diaphyseal fractures has always been a controversial one as there are two types of osteosynthesis techniques accepted worldwide, using plates and screws or intramedullary nails, each with their followers and critics, the current literature stating very similar postoperative results statistics.

Choosing the right implant and operative technique is made by taking into account a multitude of factors from which we can remind patient age, type of fracture, the surgeons experience and not last the equipment available in the surgical department. Therefore, there is no gold standard for using a certain type of implant for these types of fractures, many of which, even though are classified identically, can be surgically solved using different types of osteosynthesis procedures and devices.

The following Paper is divided into two distinct parts, a General Part in which all the known and the newest information published in the scientific field, regarding osteosynthesis of long bones diaphyseal fractures, is presented in relevance to the study direction. The Special Part contains three different clinical and experimental studies which have the purpose to compare the results obtained in a level one Orthopaedic and Traumatology centre after surgically treating diaphyseal fractures of the humerus, femur and tibia, using the two main osteosynthesis types of procedures and implants, intramedullary nails or plates and screws.

Special Part

STUDY I – Osteosynthesis in diaphyseal fractures of the humerus, femur and tibia

Material and methods

This study provides a retrospective analysis of the electronic database of patients admitted and treated surgically in a level one clinic: Orthopaedics and Traumatology I in the Timisoara County Clinic Emergency Hospital. The study selected the patients treated between 1 January 2016 and 31 December 2017, resulting in a initial number of 4480 medical files, from which were extracted manually discharges coded as fractures, resulting in a number of 1691 medical files. After furthermore selection by the anatomical segment fractured, a number of 1315 of cases of humerus, femur and tibia fractures were identified. From this point on only the files coded with the following diagnostics were selected, using the ICD-10 list : S42.3 (Humeral diaphyseal fracture), S72.3 (Femoral diaphyseal fracture), S82.21 (Tibial and fibular diaphyseal fracture) and S82.28 (Other diaphyseal tibia fractures), resulting in 268 patients corresponding to the criteria of this study, patients that were diagnosed with diaphyseal fractures of the humerus, femur and tibia, treated surgically using either closed reduction and internal fixation with intramedullary nail or open reduction and fixation using plates and screws. They were clinically followed for 1 year postoperative, undergoing both clinical and imagistic evaluation every 3, 6 months and 1 year after fracture. Patients who did not attend to these appointments or had incomplete medical files or did not correspond to the study criteria were excluded, resulting in a final number of 219 cases.

The clinical analysis was done using the EQ-VAS and EQ-5D-3L (EuroQol Group, Netherlands) evaluation instruments.

The decision of which osteosynthesis technique to use was left to the orthopaedic surgeon, without intervening in the decisional process.

An analysis of the radiographic digital images, in standard A-P and lateral incidences of the affected anatomical segment, taken at admittance in the hospital, post-operative, at 3 months, 6 months and 1 year post-op. was done searching for the mRUS (Modified Radiographic Union Scale) bone healing signs.

Data obtained was analysed in a special data base using Microsoft Office Excel 365 (Microsoft INC, Redmond, Ca, SUA) and SPSS 21.0 (SPSS INC, Chicago, IL, SUA).

For the evaluation of the significance between central tendencies indicators we used Mann Whitney U and Kruskal-Wallis test. For numerical variables the chi-square test using the Pearson method was applied, the correlations between the numerical values were done using rho coefficient of Spearman. The comparisons between the intramedullary treated patients and the ones using plates osteosynthesis was done using the t test with a significance coefficient smaller than 0,05.

Results

The initial search reported a number of 4486 patients (57,13 % female and 42,69% male). After identifying the cases with fractures of the humeral, femoral and tibial shafts coded using the ICD-10 coding system and eliminating the incomplete files, a number of 219 cases resulted (57 humeral shaft fracture, 59 femoral shaft fractures and 103 tibial shaft fractures) (Table 2).

The average age of this lot was 56,44 years and we can observe that 54,11% of them have ages between 40 and 73 years old, but patients with ages between 18- and 51-years old account for 47,49% of total.

Patients included in the study were treated surgically using osteosynthesis with plates and screws in 128 cases and with intramedullary nail in 91 cases.

The average number of hospitalization days of the entire lot was 11,79 (std. dev. 9,25). 27 cases with multiple fractures associated with the main fracture were identified, excluding fibula fractures associated with tibia fracture.

The rate of in-hospital deaths was 1,37% (3 cases), and by 1-year follow-up it reached 1,82% (another 1 case).

Table 2. Epidemiologic data

	<i>Women</i>	<i>Men</i>	<i>Total</i>	<i>Average age</i>
<i>Humeral diaphyseal fractures</i>	29 (50,88%)	29 (49,12%)	57	56,44 ani [58-29]
<i>Femoral diaphyseal fractures</i>	36 (61,02%)	23 (38,98%)	59	57,69 ani [59-32]
<i>Tibial diaphyseal fractures</i>	30 (29,13%)	73 (70,87%)	103	47,03 ani [47-25]
<i>Total</i>	95 (43,38%)	124 (56,62%)	219 (100%)	52,21 ani [18-33]
<i>Age had a non-parameter distribution ($p < 0,05$ is considered statistically significant; Shapiro Wilk test)</i>				
<i>Results are presented as a median and a [interquartile interval]</i>				

The general complications percentage was 7,76% (17 cases) of which 5 immediate postoperative (infections), 8 late postoperative at 1 year follow up (non-union) and 4 deaths.

Analysing the cause of fractures, we observed that over 78% are due to falling from ground level or above, near 14% are due to car accidents and in a smaller percentage, 7,51% work related injuries. Overseeing the subgroups, we can see that car accidents related fractures of the femur (18,52%) are more common in compare to the main group (14,08%). Also work-related tibia fractures (13,59%) have a higher percentage than the main group (7,51%). Humeral shaft fractures were the most common after falling (87,50%).

The initial EQ-VAS preoperative score had an average value of 28,15 in the main group, the lowest value in the tibia subgroup 26,62, and the highest in the femoral fracture subgroup 29.11. The mean value recorded at 1-year follow-up was 85,02, with biggest values in tibial fracture cases 87,17 (table 5).

Table 5. Health measurement average score

	<i>Initial EQ-VAS</i>	<i>initial EQ-5D-3L</i>	<i>EQ-VAS at 1year</i>	<i>EQ-5D-3L at 1 year</i>
<i>Humerus</i>	30,00 [31-10,45]	10,03 [10-1,40]	84,70 [85-7,40]	5,95 [5-1,52]
<i>Femur</i>	29,11 [31-10,04]	12,80 [13-1,30]	81,19 [82-8,12]	6,55 [6-2,07]
<i>Tibia</i>	26,62 [28-11,74]	12,47 [13-1,62]	87,17 [88-5,80]	5,70 [5-1,23]
<i>Total</i>	28,14 [30-11,05]	11,90 [12-1,87]	85,02 [85-7,27]	5,98 [5-1,58]

Results are shown as an average – [standard deviation]

The Eq5D-3L initial score had an average value of 11,90, with the biggest values found in patients whit femoral shaft fracture (12,80) and tibia shaft fractures (12,47). Like the EQ-VAS score, it also improved at the 1-year follow-up with an average of 5,95, biggest value in tibia fracture (5,70) and lowest value in femoral shaft fracture cases (6,55). Mobility improved considerably from an initial average of 2,6 to 1,22 at 1 year follow up, with best results in femoral and tibial fracture cases. The average self-care score improved with the best scores in femoral (2,92>>1,28) and tibial (2,73>>1,09) fracture cases.

From the radiographic point of view, analysing the bone healing signs according to the mRUS criteria at all the follow-ups, no statistical differences were noted, except the 1 year follow up radiographic evaluation which suggested a better union using intramedullary nailing osteosynthesis compared to plates and screws. Other follow-ups showed no significant difference between the two types of osteosynthesis.

Table 4. Percentage of cases with radiographic signs of bone healing according to mRUS criteria

	<i>General</i>			<i>Intramedullary nail</i>			<i>Plate</i>		
	3 luni	6 luni	1 an	3 luni	6 luni	1 an	3 luni	6 luni	1 an
<i>Humerus (%)</i>	75,86	94,83	94,83	82,76	96,55	96,55	68,97	93,10	93,10
<i>Femur (%)</i>	64,41	86,44	89,83	64,71	94,12	97,06	66,67	79,17	83,33
<i>Tibia (%)</i>	77,67	91,26	95,15	81,54	93,85	96,92	71,05	86,84	92,11

Union (%)	73,97	91,32	94,06	77,34	94,53	96,88	69,23	86,81	90,11
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*Favourable results are show in percentage (%).
Radiographic evaluation was based on mRUS simplified criteria*

Osteosynthesis using intramedullary nail appears to show better results in the radiographic evaluation at 1 year follow-up after surgical treatment for humeral, femoral and tibial shaft fractures.

Functional results have shown no statistically significant differences between the type of surgical procedure.

The number of hospitalization days was directly influenced by patient age.

The average age of the study lot was directly proportioned with the health evaluation instrument score EQ-5D-3L and with the depression/anxiety criteria.

The type of osteosynthesis procedure used was correlated with the period of hospitalisation and with the radiographic signs of union at 1-year follow-up.

Study II – Haematology panel biomarkers in humeral, femoral and tibial diaphyseal fractures

Neutrophil to lymphocyte ratio (NLR) is a simple haematology panel biomarker of the inflammatory response that can be predictable of the outcome and severity in tumours, cardiovascular disease, hip fracture, and polytrauma [Templeton, Mei, Kim, Afari, Forget, Dilektasli, Wang]. However, there is no data regarding the profile of NLR in patients with diaphyseal fractures.

We aimed to analyse the NLR profile of patients with diaphyseal fractures of the humerus, femur, and tibia.

Materials and methods

We performed a retrospective analysis of our level 1 trauma centre electronic data base over two years. We searched for patients discharged with the main diagnosis of any of the following ICD-10 codes: S42.3, S72.3, S82.21, and S82.28, representing diaphyseal fractures of the humerus, femur and tibia. The search Retrieved 172 records that were individually reviewed for data consistency. As a result, 24 patients were excluded for coding errors or missing data. The haematology panel at admittance was performed using either Nihon Kohden Celtac 6500, Sysmex XT-4000i, or ADVIA 2120 analysers. We manually extracted haemoglobin value and neutrophil, lymphocyte, and platelet counts, from which we computed NLR and PLR (platelet to lymphocyte ratio) as markers of inflammation.

We then performed a cross-sectional, consecutive-case population-based study including 148 patients with diaphyseal fractures (41,9% men respectively 58.1% women). The study group was stratified for analysis purposes in three cohorts in respect to the type of the fracture: humeral 9 23.0%), femoral 9 30.4%), and tibial (46.6%). The dimensions of the cohort were calculated prior to enrolment to provide statistical power ($1 - \beta = 0.8$) with a type I statistical error probability of $\alpha = 0.05$.

Information was collected in a file type Microsoft Office 365 Access database (Microsoft INC, Redmond, CA, USA) and was analysed using SPSS v.17 (SPSS INC, Chicago, IL, USA).

Results

In the studied group, there were significant differences between the types of fractures regarding the patient's age ($p<0.001$), duration of admission ($p<0.001$), haemoglobin value (0.002), and lymphocytes ($p=0.030$). femoral fracture was associated with a higher age and a longer admission duration, in contrast with patients with tibial fracture, cohort in which we observed the lowest median age (41 years). Patients with tibial fracture had the highest haemoglobin and lymphocyte value. The differences in NLR between the three studied subgroups were not significant ($p=0.067$), the highest value being observed in patients with femoral fracture (5.6) in contrast to patients with humeral fracture (4).

We found a significant association between gender and the type of fracture: 52,9% of patients with humeral fracture and 57.8% with femoral fracture being women in contrast to only 26.1% of the patients with tibial fracture ($p=0.001$; Pearson's chi square test).

Regarding the stratified subgroup analysis, the only significant association found was between NLR and duration of admission in patients with femoral fracture (Spearman's $r = -0.308$; $p<0.001$).

To the best of our knowledge, this is the first analysis of NLR and PLR in patients with humeral, femoral, and tibial diaphyseal fractures. The differences in NLR between the three studied subgroups were no significant ($p=0.067$), the highest value being observed in patients with femoral fracture (5.6) compared to patients with humeral fracture (4). When compare with controls, all three fracture types had significantly higher neutrophil numbers and NLR and lower thrombocyte numbers. We believe this can be explained by the impact of the fracture on the inflammation status.

NLR are elevated in femur diaphyseal fractures compared with tibia and humerus, up to cut-off values with negative prediction outcomes in malignant and cardiovascular patients. PLR follows a similar trend. Increased NLR are predictive of longer hospital admissions for femur fractures.

Table 15. Correlation between NLR and PLR depending on type of fracture.

Days of admission	r (NLR)	p (PLR)	r (NLR)	p (PLR)
Humerus	0.262	0.135	0.181	0.304
Femur	-0.308	0.039	-0.200	0.187
Tibia	-0.004	0.975	-0.058	0.485

Study III - Tissue alterations in contact with osteosynthesis implants.

Materials and methods

The present study is a retrospective analysis of data acquired from the processing of paraffin imbedded tissue obtained in open surgery for removal of osteosynthesis implants at 14 to 18 months after primary osteosynthesis from the cases mentioned earlier. We opted for this type of study because it allowed a thorough selection of the cases with all the required elements known for a complete prognostic appreciation. From every bloc of paraffin, serial sectioning was performed for the purpose of colouring using morphological, immunohistochemistry methods.

The tissue samples were surgically extracted during open surgery, after which were processed according to histological techniques. Harvesting was done with great haste

because of the fast-installing post-mortem biochemical alterations which appear faster than the structural changes.

The standard coloration methods used in the present study were haematoxylin-eosin, based on Mayer haematoxylin and watered eosin, and Masson trichrome protocol, based on aniline blue.

The analysis was based on searching the types of normal and pathological tissue, the cellularity character, the presence and aspects of bone tissue, inflammatory reactions, existence of necrosis and disposition and type of blood vessels.

Results

Conventional morphologic evaluation of biopsy of tissue surrounding devices used in surgical interventions for diaphyseal fractures found certain aspects. First, it reminds of the importance of the development of collagen fibers, organized in thick fascicles.

In cases with old, neglected fractures, bone fragments and aberrant calcifications are the most visible aspect. Also, numerous new blood vessels appear following inflammatory angiogenesis. We could not find certain aspects related to the type of surgical method used.

In the analysis of the tissue fragments found in the vicinity of intramedullary nail we evaluated soft and hard tissue in the form they appeared after decalcification. In these cases, biopsies included tissue found externally from the bone, extended fragments of compact haversian bone tissue with or without reparatory phenomenon or medullary tissue.

Worth mentioning is the fact that hematogenic bone marrow was not found on neither one of the pieces, a possible explanation could be the short time from the moment of fracture and tissue prelevation.

Two of the cases operated using intramedullary nailing technique reported granulation tissue with numerous cellularity consisted of lymphocyte, plasmocyte, macrophage and granulocyte in specially neutrophils. Many of the blood vessels surrounding these areas have aspects of neoformation, signalling proliferative activation.

Bone tissue fragments included in the specimen presented inactive periosteum, most of the times hyalinized, with calcified and basophilic bone matrix. Haversian systems were found in 75% of cases, containing all the known structural elements.

GENERAL CONCLUSIONS

Diaphyseal fractures of humerus, femur and tibia are usually the result of a high energy, violent and traumatic force.

After producing a fracture, the alteration in the structural integrity of the bone causes a reparatory response coordinated by the central nervous system through complex neurological, endocrinal and inflammatory changes.

Thus, a fracture must not be interpreted as solely a bone related illness, but a far more complex pathology involving multiple organs and systems.

1. In the Special Part of the Thesis we followed the evolution of diaphyseal fractures of long bones, relying on studies and statistical results, paraclinical and histological aspects through a study of the results obtained in a level 1 orthopaedics and traumatology centre in the surgical treatment of diaphyseal fractures of humerus, femur, and tibia using osteosynthesis with plates and screws or intramedullary nail.

- the radiographic evaluation at 1-year follow-up after osteosynthesis using intramedullary nail for diaphyseal fractures of humerus, femur, and tibia showed the best results;

- the type of osteosynthesis procedure used correlated with the time of admission and the radiographic signs of healing at 1-year follow-up;
- functional results did not show statistically significant differences between the two types of surgical procedures;
- a longer admission time was associated with a bigger chance of non-union at 1-year follow-up after osteosynthesis using plates and screws in diaphyseal fractures
- the number of admission days associated with the surgical treatment of humeral, femoral and tibial shaft fractures was directly influenced by the age of the patients;
- the patient's age was proportionately influenced with the health evaluation score EQ-5D-3L and with the depression/ anxiety dimension.

2. In our study we performed a haematology analysis to investigate the lymphocyte to neutrophil ratio in patients with diaphyseal fractures of the humerus, femur, and tibia:

- NLR is a simple haematology panel biomarker of the inflammatory response and can be a predictive and severity factor in other illnesses (tumours, cardiovascular disease, polytrauma);
- the conclusions of this study show that NLR has higher levels in diaphyseal fractures of the femur, compared to tibia and humerus, and at certain border levels it can be a negative prediction factor for functional results;
- PLR (platelets to lymphocyte ratio) have a similar behaviour in the studied lot;
- high values of PLR are a predictive factor for diaphyseal fractures of long bones;
- to our knowledge, this study which was published in the prestigious *International Orthopaedics* is the first analysis of NLR and PLR in patients with humeral, femoral and tibial shaft fractures.

3. A study regarding tissue alterations in the vicinity of intramedullary nail or plates and screws implants was conducted in the Laboratory of Histology of the University of Medicine and Pharmacy "Victor Babes" from Timisoara under the coordination of prof. dr. Marius Raica.

Bone tissue was harvested during the surgical extractions of osteosynthesis implants at 14-18 months after primary osteosynthesis was performed (a total of 22 pieces), and based on that research we concluded:

- alterations of the soft tissue are unspecific, characterized by inflammatory aspects of different intensity;
- the connective tissue in the vicinity of the implant develops focal aspects of mesenchymal type, rich in star-shaped fibroblasts;
- the types of lesions observed could not be associated with the surgical technique used in the treatment of the diaphyseal fractures;
- two of the cases presented granulation tissue in association with rich inflammatory angiogenesis;
- areas of mature osteoid bone tissue was found in only one case, without association with remodelling elements.