INTRAOPERATIVE BLEEDING IN PATIENTS WITH OSTEOGENESIS IMPERFECTA TYPE 3 DURING FEMORAL RODDING WITH FASSIER-DUVAL TELESCOPIC NAIL: OBSERVATIONS, RISK FACTOR ANALYSIS AND HYPOTHESIS OF PREVENTION.

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ABSTRACT

Blood loss during femoral nailing surgeries in patients with OI is a serious problem. In order to define the predictive risk factors, a retrospective analysis was conducted on a sample of 23 patients with OI type 3, treated from January 2013 to December 2015, for femoral fracture or femoral deformity correction with the Fassier-Duval telescopic nail.

There was an average 197cc of blood loss. Seven blood transfusions were carried out post-operatively following an average bleeding amount of 379cc. The average blood loss was associated with age, the presence of abnormalities in platelet function, the number of osteotomies and the intake of Bisphosphonates.

To test the influence of potential predisposing factors, the following aspects resulted significant as predictive risk factors for intraoperative bleeding: young age, terapy whit bisphosphonates and a larger number of osteotomies during the surgical procedures.

Keyword Osteogenesis Imperfecta**,** Surgical Blood Loss**,** Intramedullary Nailing**,** Risk Factors

INTRODUCTION

Osteogenesis imperfecta (OI) is a rare multi-systemic disease, a hereditary pathogenesis that affects the connective tissue, characterized by various clinical manifestations, including frequent fractures and deformities, which require the need for frequent orthopedic procedures [1, 2, 3, 4]. The classification has been updated in 7 types of OI [5]

The surgical treatment is negatively influenced by clinical features such as: osteoporosis, the presence of deformities and bone changes caused by bisphosphonate therapy. [6, 7]

Furthermore, the comorbidities are able to influence the anesthesia procedures with evidence of the following: the risk of hyperthermia [8, 9], an increased metabolic activity of the leukocytes and a decrease of platelet function [10, 11]. Platelet anomalies have been associated with an elevation of the serum pyrophosphate originating from the platelets during clotting, even if the causality with the platelet dysfunction has not yet been established [12, 13, 14].

MATERIALS AND METHODS

Out of a population of 485 patients with Osteogenesis Imperfecta, in treatment at the Center for Congenital Osteodystrophies of the Policlinico Umberto I in Rome, we selected a sample of 23 non-consecutive patients affected by OI type 3, who underwent surgical femoral fixation with Fassier Duval (FD) telescopic nails, from January 2013 to December 2015.

A retrospective analysis was performed with the aid of charts, files and reports

related to the surgery, the anesthesia and the hospitalization, and of those factors associated to possible blood loss: age, bisphosphonate therapy, haematochemical tests, indication for surgery (fracture or deformity correction), number of osteotomies, surgical time, blood loss forecasting, actual intra-operative bleeding and possible blood transfusions.

A single operator (PP), with an already acquired specific learning curve, treated, by means of internal fixation with the FD telescopic nail, 9 patients for femoral fractures and 14 patients for femoral deformities that needed correcting (primary or secondary to a previous fracture).

The patients, 10 females and 13 males, were aged between 6 and 13 years old.

Osteotomies were performed in all 14 cases with deformities and in 2 cases with a fracture, with an average of 2 osteotomies per segment. In the remaining 7 cases of fracture, the fracture itself was exploited to correct any deformities, so no osteotomies were performed.

At the time of surgery, 14 patients (61%) had been in terapy with Neridronate (Nerixia®, 2mg / kg IV dose every 3 months) for at least one year. In the patients scheduled for osteotomies for deformity correction, we suspended the therapy with bisphosphonates for 4 months, in order to avoid delays in consolidation and pseudo-arthrosis. [15]. The remaining 9 patients (39%) never underwent treatment protocol with bisphosphonates.

Among the parameters checked, the intraoperative hemochrome was unable to provide a precise indication on the actual hemoglobin count, as it does not take into account the degree of dilution of the fluids administered, and the amount of liquids attracted by the administered plasma substitutes.

An assessment of the blood loss is obtained from the surgical notes and the anesthesia records, by calculating the sum of the blood aspirated with that lost with the gauzes or present on the surgical drapes.

In order to obtain an estimate of the intraoperative blood losses, one must resort to a calculation based on an algorithm, which evaluates the ratio between the effective blood loss divided by the total blood volume expected per age and weight. This way, the gamma distribution is applied in the prediction of blood loss during the specific surgery in relation to the patient's body surface area, and to the possible predisposing factors or risks known per pathology [16, 17]

The statistical analysis was performed using the SPSS 20.0 statistical software. The chi-square test was used for the analysis of discrete data and the associations between variables. Comparisons between averages were performed with the t-test for two independent variables and the ANOVA test for multiple variables.

RESULTS

The data collected and analyzed values were related to bleeding. TABLE 1.

The surgical times were between 50 and 140 min (average duration 89,56 min) and the duration of hospitalization was from 1 to 5 days.

The average blood loss was 237,39cc from 100 cc to 700 cc (standard deviation (SD) of 195,03 cc). The estimate of the average blood loss was equal to 0.12 gamma (SD 0.112 gamma with intervals of 0.04-0.4).
In 7 of the cases (30.4%) it was necessary to perform post-operative transfusions, due to an average blood loss of 502,85 cc. and an estimated loss *of 0.271 GAMMA.*
No difference was found in the actual or estimated blood loss when comparing the procedures for deformity correction to the reduction and Intramedullary fixation for acute fractures procedures. However, if the synthesis of the fracture also required a corrective osteotomy, the bleeding increased. The association between surgical times and the actual and estimated blood loss was not significant (P = 0.36). Older patients (> 10yo) had a statistically significant (P = 0.07) lower average blood loss. TABLE 2. A growing number of osteotomies has led to a significant increase in the average effective blood loss (P = 0.05). Patients who had never been treated with bisphosphonates showed a statistically significant higher rate of bleeding (P=0.05) TABLE 3 - 4

DISCUSSION

Patients with OI type 3 are considered at high risk of blood loss during surgery due to capillary fragility and an altered platelet function [11, 12, 13].
In addition to this predisposition, there are added risk factors that must be considered when planning a femoral fixation surgery with the FD telescopic nail.
The patient's age is inversely related to the blood loss, which is better tolerated in older patients because of a greater total volume of blood circulating.
The perioperative blood loss was almost identical in both the treatment of fractures and the osteotomies for the correction of deformities 18
The bleeding, however, increased in cases of fractures that required additional corrective osteotomies (the bleeding of the fracture is, in fact, added to the bleeding in the osteotomy sites).
In patients who had never been treated with bisphosphonates, the bleeding was greater than in patients treated with bisphosphonates (Neridronate) for at least one year. Hypothetically, the effect of the bisphosphonates on the bone, in particular the reduction of the medullary canal and thickening of the cortex, can reduce the amount of cancellous bone and thereby reduce the rate of bleeding.
In addition, by inhibiting the farnesyl pyrophosphate synthase (FPPS) and diminishing the prenylation of many plasma proteins, including the methylenetetrahydrofolate reductase (MTHFR), the bisphosphonates could lead to an alteration of the coagulation cascade. [19]

CONCLUSION

The number of osteotomies, the patient's age, the alterations in platelet function and the intake of bisphosphonates for at least a year, seem to be the best predictive factors for blood loss. The correlation found with the intake of bisphosphonates,

capable of inhibiting the action of the FPPS, thus influencing coagulation, requires further prospective studies with research of the MTHFR mutation in patients whit Osteogenesis Imperfecta Type 3 who underwent surgical procedures.

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Conflicts of interest.
None declared.

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	AGE	WEIGHT KG	SURGERY Fracture Deformity	TIME of SURGERY Minutes	N of OSTEOTOMY	BISPHOSPHONATE Y/N	N TRASFUSION	REAL BLOOD LOSS ML	ESTIMATE BLOOD LOSS GAMMA
1	5	19	F	50	0	yes	0	100	0,07
2	6	21	F	50	0	yes	0	110	0,06
3	8	24	F	70	0	yes	0	100	0,05
4	12	36	F	60	0	yes	0	110	0,04
5	10	30	F	60	0	yes	0	100	0,04
6	9	27	F	80	0	yes	0	100	0,05
7	11	33	F	70	1	yes	0	110	0,04
8	8	24	F	70	1*	no	1	300	0,16
9	10	30	F	80	1	yes	0	210	0,1
10	9	27	D	70	2	yes	0	110	0,05
11	7	23	D	80	2	no	0	110	0,06
12	7	23	D	80	2	no	1	400	0,23
13	8	24	D	90	3	yes	1	420	0,26
14	10	30	D	90	3	yes	0	120	0,05
15	11	33	D	90	3	no	0	130	0,05
16	10	30	D	100	3	yes	0	130	0,05
17	11	33	D	120	3	no	0	120	0,05
18	7	23	D	140	3	no	1	700	0,4
19	8	24	D	120	3	no	1	600	0,33
20	7	23	D	120	3	yes	1	600	0,34
21	10	30	D	130	3	no	0	130	0,05
22	10	30	D	120	3	yes	0	150	0,06
23	12	36	D	120	3	no	1	500	0,18
M	**8,95**	-	**9 . 14**	**89,56**	**1,82**	**14 - 9**	**7**	**237,39**	**0,120**
DS	**1,91**	-	-	**26,71**	**1,30**	-	-	**195,03**	**0,112**

TABLE 1 Summary (age, weight, indication for surgery, time of surgery, number of osteotomy, therapy or not with bisphosphonates, number of transfusion, real and estimate blood loss) of our population (23 patients with OI type 3).
M media; DS Deviation Standard

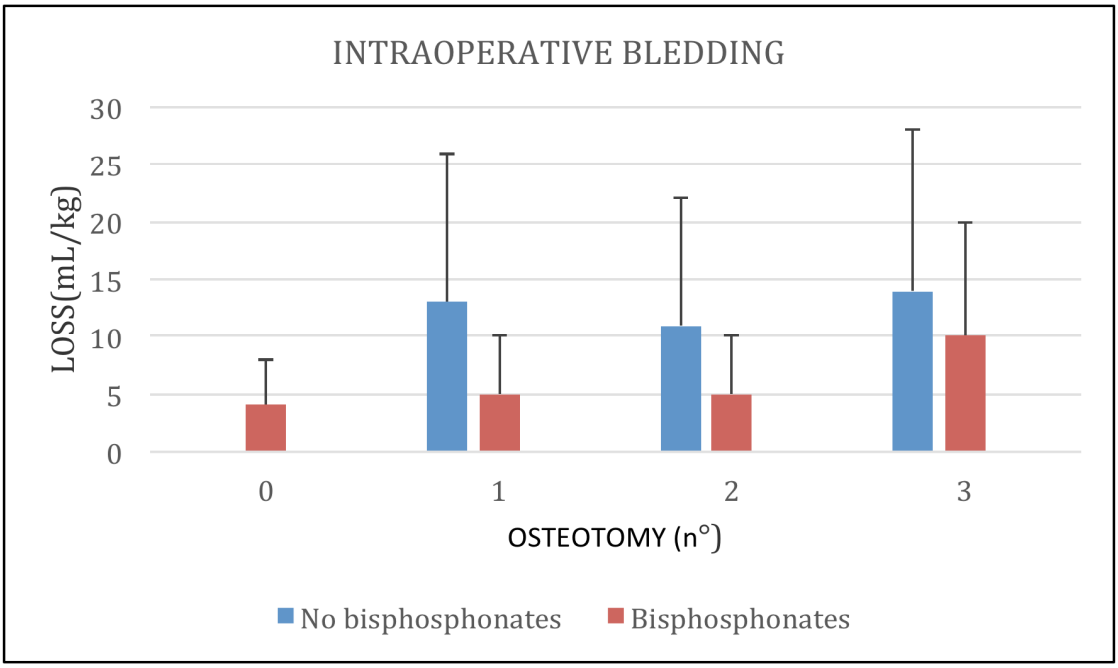

TABLE 3 blood loss related to number of osteotomies and bisphosphonate therapy

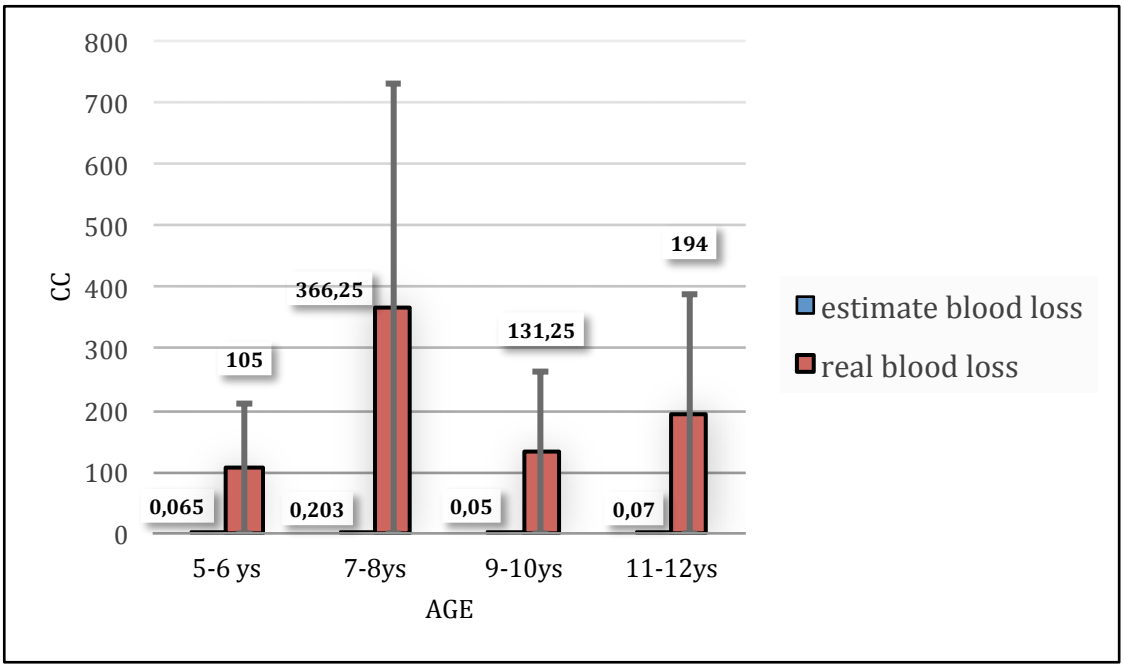

TABLE 2 correlation between age, real and estimated blood loss

	AGE >10	AGE<10	n osteotomy 0-1	n osteotomy 2-3	bisphosphonates	No bisphosphonates
REAL BLOOD LOSS	164,54	608,33	136,6	301,4	176,4	332,2
ESTIMATE BLOOD LOSS	0,06	0,17 (P 0,07)	0,06	0,15 (P 0,05)	0,09	0,16 (P 0,05)

table 4 correlation between age, bisphosphonates terapy, osteotomy and real and estimated blood loss