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ORIGINAL PAPER

Improved patient blood management and cost saving in hip replacement surgery through the implementation of pre-operative Sucrosomial® iron supplementation: a quality improvement assessment study

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Abstract

Purpose To compare post-operative recovery of prosthetic hip surgery patients with or without the implementation of iron supplementation with a new highly absorbable oral iron formulation.

Methods Observational retrospective quality improvement assessment conducted on patients who had undergone elective prosthetic hip surgery (first implant) with ferritin < 100 mcg/dl and Hb values between 13 and 14 g/dl for men and 12 g/dl and 13.5 g/dl for women, or having ferritin levels > 100 mcg/dl but C-reactive protein (CRP) > 3 mg/l and transferrin saturation (TSAT) < 20%, which together are suggestive of functional iron deficiency. The analysis compared a group of non-anaemic patients having ferritin levels > 100 mcg/l to two groups of patients with iron deficiency, of which only one received iron supplementation. Measurements included haemoglobin levels, length of hospital stay, and number of transfused patients/blood units.

Results Patients with iron deficiency supplemented with Sideral® Forte compared to non-supplemented patients showed a smaller decline in post-operative Hb (9.7 ± 1.24 g/dl vs 8.4 ± 0.6 g/dl), required shorter hospital stay (4 vs 6.5 days) and less blood transfusions (0 in the iron-supplemented group vs 7 units in the non-iron-supplemented group), yielding an overall savings of 1763.25 €/patient.

Conclusions Pre-operative sucrosomial iron supplementation at least 4 weeks prior to elective surgery in non-anaemic patients limits the drop in post-operative Hb levels, determining higher post-operative haemoglobin, quicker post-surgical recovery, shorter hospitalisation, and decreased surgery-related costs.

Keywords Patient blood management · Peri-operatory haemoglobin levels · Prosthetic hip surgery · Sideral® Forte · Oral sucrosomial iron

Introduction

In recent years, there has been growing attention towards optimal patient blood management (PBM) to limit the overuse of red blood cell (RBC) transfusions (both allogenic and autologous) and improve outcome of patients undertaking major surgery through a faster clinical and functional recovery. The correlation between anaemia and major risks is independent from the type of surgical interventions [1]. However, compared to non-anaemic patients, anaemic patients have a 42% higher risk of mortality and a 35% higher risk of serious complications [1].

Several studies have evidenced the important role of perioperative concentrations of haemoglobin (Hb) in patients undergoing orthopaedic surgical procedures, demonstrating that longer hospital stay, higher RBC transfusion rates, and higher mortality are linked to low Hb values and anaemia [1–6].

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Because pre-operative anaemia appears to be also related to poorer prognosis, timely prevention of post-operative anaemia and iron stores is pivotal. In the case of orthopaedic surgery, many patients are already anaemic prior to admission (25%) either due to chronic disease [6–8], underlying illness burden, and bleeding, or following pre-surgery blood drawing in view of autologous transfusions. Haemoglobin may, however, be subject to further fluctuation during hospitalisation due to interventions such as fluid hydration after admission [3, 6]. During operation, bleeding and haemodilution largely contribute to decrease Hb concentration, with anaemia ranging between approximately 51 and 80% of patients after elective orthopaedic surgery [6]. In general, compared to other types of surgery, orthopaedic surgery implies substantial blood loss (generally approximately > 1 l or 20% of blood volume) that affects patient outcome [9]. Moreover, patient outcome can be further influenced by pre-operative iron deficiency, which is associated to a greater degree of fatigue seven days after surgery [10], and pre-surgical hospitalisation-induced anaemia (defined as Hb < 9 g/dl) which affects approximately 37% of patients who are already anaemic [8]. In recent years, the aspect of blood loss in hip replacement has been addressed through several approaches [11–15]; however, despite the interesting results, these appear to solve the issue only partially and not to significantly improve early patient recovery—especially when these methods are implemented alone and without proper management of the patient's haematopoietic profile.

A prospective cohort study on peri-operative anaemia in patients undergoing surgery for hip fractures demonstrated that higher pre-operative haemoglobin levels were associated with shorter hospital stay and lower odds of death and readmission; likewise, higher post-operative Hb levels were also associated with shorter hospital stay and readmissions [3]. Another study on the implementation of a pre-operative haematinics and RBC transfusion protocol including pre-operative iron supplementation lead to lower RBC transfusion rates, with the difference remaining significant after patient's stratification according to pre-operative Hb > 13 g/dl [2]. A randomised study on iron preload for knee and hip replacement described the 4-week pre-operative iron supplementation in non-anaemic patients with Hb > 12 g/dl, and showed that, despite no pre-operative rise in Hb, the iron supplementation had contributed to maintaining higher Hb concentrations in the immediate post-operative period [16]. Pre-surgical oral iron supplementation was also studied in other surgical settings such as colorectal surgery and showed to increase Hb levels before admission and limit the post-operative Hb drop in anaemic and non-anaemic patients, decreasing the need for RBC transfusion peri-operatively among patients who had received iron supplementation [17].

In recent years, much effort has been spent towards outlining a proper PBM through several guidelines [18–20], calling for a joint effort to minimise the patient's potentially fatal risks involved with unnecessary RBC transfusions or transfusion-related treatments. In line with the objectives of PBM (optimization of pre-operative haemoglobin levels, implementation of blood-sparing techniques, and standardisation of RBC transfusion practices), our unit introduced a pre-operative protocol of iron supplementation with highly absorbable oral sucrosomial iron in non-anaemic patients scheduled for elective surgery. The present study aimed to assess improvements linked to the implementation of such protocol, in particular, in terms of changes in peri-operative Hb levels and of cost savings per patient.

Materials and methods

The present is a retrospective quality improvement assessment study following the implementation of the PBM protocol, on a population of patients who underwent elective prosthetic hip surgery (first implantation) during 2016, at the Hip and Prosthetic Orthopaedics Unit at Humanitas Research Hospital in Rozzano (Italy).

The study considered a representative population of patients admitted for elective hip surgery. Patients who had post-surgical infections, which are known to affect most biochemical parameters of iron status, thus representing a clear confounder, were excluded. Due to the fact that elective surgery at our Unit was only performed on patients with suitable clinical conditions, these cohorts did not include patients with anaemia or having major comorbidities (e.g., diabetes, heart disease NYHA class < 2, coronary disease, kidney or liver failure), haematological diseases, malignancies, or on anti-platelet or anticoagulant therapies.

In 2016, all patients at our unit were managed according to a standard pre-operative clinical practice protocol for prosthetic hip surgery, which foresaw a first patient visit at 28–35 days prior to the scheduled surgery and a routine screening for prosthetic elective surgery plus full routine blood tests. Based on our Unit's patient management decisional algorithm, patients presenting at screening with anaemia (defined as Hb levels < 13 g/dl for men and < 12 g/dl for women) or other relevant health problems were discarded for surgery and were referred elsewhere to address any pre-existing health issues that could have compromised the patient's physical fitness for elective surgery. Later in the year, in line with new evidence emerging on PBM [18–21], the protocol introduced the routine ferritin measurement in patient screening and extended admission to surgery also to patients with functional iron deficiency with values ferritin < 100 mcg/l and 13 < Hb < 14 g/dl for men and 12 g/dl < Hb < 13.5 g/dl for women, or having ferritin levels > 100 mcg/l but C-reactive protein (CRP) > 3 mg/l and transferrin saturation (TSAT) < 20% [5]. For this group, iron supplementation was recommended, while all

other aspects of patient management such as RBC transfusion threshold and surgical procedures remained the same as before.

Supplementation consisted in Sucrosomial® iron (Sideral® Forte), one 30 mg capsule/day for three to four weeks prior to surgery (depending on when patient was scheduled for the pre-operatory screening visit). Sucrosomial® iron was selected for the protocol in virtue of its extremely high iron bioavailability [22]. Being covered by phospholipids plus sucrose esters of fatty acids matrix, this formulation allows a higher absorption of iron compared to ferrous sulphate and avoids typical gastrointestinal side effects such as abdominal pain, constipation, vomiting, heart-burn, oxidative reaction, and diarrhoea caused by traditional oral iron formulations and/or IV iron formulations. Its high tolerability and the improvement of the patient's anaemic condition in terms of serum iron, haemoglobin, and ferritin have been confirmed by several studies [22–27]. Moreover, oral sucrosomial iron has been demonstrated to be comparable, in terms of increase in Hb values, to intravenous iron therapy both in cancer and nephropathic patients [7, 23–26], without the risks brought by IV infusion [28].

All measurements considered in the study period were performed within the same hospital laboratory. Hb levels were measured 28–35 days prior to surgery, one day after surgery, at the discharge, and 30 days after surgery by department lab and the Hospital's central reference lab using Pentra DF Nexus and Pentra DX Nexus (Horiba, Kyoto, Japan) platforms. The surgical procedures were performed following the tissue sparing surgery technique [29–31]. Throughout the observation period considered, no other changes were undertaken in the performance of routine clinical or operating procedures for this type of elective hip replacement surgery, thus excluding any changes in cell savage (which had never been performed), in the amount of tranexamic acid infusion (1 g) used, and in peri-operative fluid optimisation procedure. Patient management, blood transfusion policies and transfusion thresholds, and surgical staff also remained unaltered throughout the time period examined. The threshold set for post-operative RBC transfusion was set at either Hb < 7 g/dl or at Hb < 9 g/dl when tachycardia was present [9, 21]. Criteria for delaying patient discharge were pain and Hb < 8 g/dl, which negatively affect the patient's functional ability to perform daily routine activities.

Data on socio-demographic characteristics, clinical parameters, vital signs, comorbidities, inflammatory markers, and clinical status prior to admission and upon discharge had been previously collected in the patient clinical records and the hospital electronic database, as foreseen by hospital management procedures. The data specifically considered for the purpose of the study reported herein were pre- and post-operative Hb levels, RBC transfusion units received, and length of hospital stay (LOS). Other parameters of iron homeostasis, such as transferritin, were not considered as their evaluation was beyond the scope of our study.

The study assessed iron status profile of patients with iron deficit by comparing values of patients receiving oral sucrosomial iron (+ iron group) with those of patients who responded to the same criteria but who did not receive iron (either due to lack of patient adherence to supplementation protocol or to the attending physician's lack of awareness on benefits of iron supplementation (− iron group) and then with patients with no iron deficiency (Group C). Patients in the three groups were matched for demographic and clinical characteristics (same intervention type, blood loss profile, lack of comorbidities, ASA 1 and 2); Table 1.

This approach was followed for both the clinical and economic evaluations. Accordingly, outcomes measured were

Table 1 Demographic and clinical characteristics of patient population, divided per group

General characteristics	Hb > 14 Ferritin > 100	13 < Hb < 14 Ferritin< 100	
Patient groups/parameters	(+ Iron)	(− Iron)	
	Group A	Group B	Group C
	n = 100	*n* = 100	*n* = 100
Age, year (mean ± SD)	68.8 ± 9.4	68.4 ± 9.5	68.2 ± 8.9
Sex (*n*, M/F)	44/56	43/57	48/52
Weight, kg (mean ± SD)	79.4 ± 10.34	80.3 ± 11.24	81.2 ± 10.11
Height, cm (mean ± SD)	172.42 ± 7.8	172.93 ± 8.02	172.88 ± 8.12
ASA classification/or functional mobility score	I/II	I/II	I/II
Blood parameters			
RBC (mean ± SD)	4.58 ± 0.28	4.27 ± 0.46	4.28 ± 0.42
CRP	< 0.4	< 0.4	< 0.4
Medication			
ESA	2	0	0
Anti-inflammatory	31	25	22

changes in peri-operative levels of Hb levels, in LOS and, in percentage and units of RBC transfusions. The items considered in our study for quantifying saving per patient included direct patient management costs per day of hospital stay (€ 700 in 2016), RBC units transfused per patient (€ 475 per RBC unit transfused) [32], and one 21- or 28-day cycle of iron supplementation (€ 20/box of 20 capsules) divided by the total number of patients.

Patient sample was calculated by power analysis based on the frequency of the events examined, in consideration of transfusion frequency, Hb levels, and costs.

Considering the primary objective being the reduction of haemoglobin, we expected a reduction of 0.2 g/dl in the group treated with iron and of about 0.3 g/dl in the no iron group. Considering a foreseen standard deviation of 0.3 g/dl with an error α of 0.05 and with a power of 8.8, the total number of patients to be enrolled was calculated to be 186 (93 per treatment arm). In order for the treatment to be considered different, a significance of 0.00019 will have to be detected, in accordance with the Alpha spending function and O'Brien-Fleming function [33].

Means with standard deviations and medians with interquartile ranges were calculated as appropriate. Variations in Hb post-surgery concentrations and in the delta Hb (difference between the Hb pre and post intervention) were detected by two-way ANOVA analysis using Sidak's multi comparisons test. Paired *t* test, one and two-tailed were used to detect significant difference in Hb concentrations between the day after surgery and the values measured three weeks before surgery, while the correlations between these variables were tested using the Pearson linear correlations test. The level of significance was set at $P < 0.05$.

Ethical considerations

The present study was performed in accordance with the principles outlined in the Declaration of Helsinki. Being an initiative of a pre-operative protocol standardisation established at the Orthopaedics Department, the study was presented to the local Ethics Committee of the Humanitas Research Hospital for approval and patients' clinical data were handled as agreed by patient's informed consent.

Results

The overall study population at baseline had a mean age of 68.5 years (± 6.6), had comparable haemoglobin at pre-hospitalisation visit, and was representative of the typical patient population of candidates for elective prosthetic hip surgery described in literature: mean weight 78.0 Kg ± 8.2; mean height 172.3 cm ± 3.54 (Table 1); no important comorbidities and no concomitant treatments other than non-steroidal anti-inflammatory drugs were present.

As to the iron-related values after surgery (Table 2), post-operative Hb levels in the (+ iron) group were 9.7 ± 1.24 g/dl vs 8.4 ± 0.82 in the (− iron) group with a Hb difference of 1.3 ± 0.9 g/dl between the two groups ($P \leq 0.0001$, two-way ANOVA). Patients in the (+ iron) group were discharged earlier, after 4 days from surgery with a mean Hb value of 11.2 ± 1.37, compared to Hb 9.6 ± 1.16 at discharge after 6.5 days from surgery for (− iron) group. Moreover, while Hb in patients receiving oral iron (+ iron) had returned close to baseline values within 30 days from surgery (13.3 ± 1.54 mg/dL at 30 days; 13.4 baseline), this did not happen for the (− iron) group (10.2 ± 1.19 at 30 days; 13.5 at baseline). This aspect also reflected on the number of transfused units: seven in the (− iron) group vs none in the (+ iron) group. Also, LOS in (+ iron) group was 2.5 days shorter compared to those in (− iron) group.

Finally, comparison between Group A (+ iron) and Group C (no iron deficiency) revealed that, the mean Hb value achieved at 30 days from discharge was higher in the former group (13.3 ± 1.5 vs 12.8 ± 1.4) despite its lower mean baseline Hb values (13.4 ± 0.2 in Group A vs 14.8 ± 0.28 in Group C). Days of hospital stay were the same in both groups, A and C.

As to cost analysis (Table 3), the comparison of the three representative subgroups evidenced lower expenses in Group A (+ iron) compared to Group B (− iron), both in terms of

Table 2 Clinical parameters related to iron status

Hb range and ferritin	13 < Hb < 14 Ferritin < 100 (+ Iron) Group A	13 < Hb < 14 Ferritin < 100 (− Iron) Group B	Hb > 14 Ferritin > 100 Group C
Patients *n* (%)	100	100	100
Hb baseline, g/dL (mean ± SD)	13.45 ± 0.26	13.5 ± 0.21	14.8 ± 0.28
Ferritin, mcg/dL (mean ± SD)	65.4 ± 12.37	66 ± 10.25	160.5 ± 25.73
Hb 1 day post-surgery, g/dL (mean ± SD)	9.7 ± 1.24	8.4 ± 0.82	10.5 ± 1.26
Hb discharge, g/dL (mean ± SD)	11.2 ± 1.37	9.6 ± 1.16	11.3 ± 1.46
Hb 30 days post-surgery, g/dL (mean ± SD)	13.3 ± 1.54	10.2 ± 1.19	12.8 ± 1.43
RBC transplants (*n*)	0	7	0
LOS, days (mean ± SD)	4	6.5	4

Table 3 Cost analysis based on the three subgroups of patients

	(+ Iron) Group A Iron deficiency	(− Iron) Group B Iron deficiency	Group C No iron deficiency
Patients *n*			
	100	100	100
RBC transfusion costs/patient (€)			
n. sacks	0	7	0
€ 475/transfusion sack	0	3.325	0
Sucrosomial iron costs/patient (€)			
n. boxes	1/patient	–	–
€ 20/box 20 capsules	€ 20.00	0	0
Hospitalisation costs/patient (€)			
Mean days	4 days	6.5 days	4 days
€ 700/day	2.800	4.550	2.800
Total cost per patient (€)			
	2.820	7.875	2.800

blood transfusion costs and of LOS. The most expensive item was hospitalisation per patient and accounted for € 4.550/patient in (− iron) group against the € 2.800 in (+ iron) Group. As to costs for RBC transfusion, this expense item—in this subset analysed—was only found for the (− iron) groups, while the cost was nil for patients in the (+ iron) and C groups. The difference in cost registered between Group A and Group B (sharing the same characteristics and baseline Hb) calculated as spread out on 100 patients was 1763.25 €/patient.

Discussion

The present study aimed to evaluate the benefits gained by implementing a peri-operative iron supplementation protocol in non-anaemic patients scheduled for elective hip surgery. Overall, results evidenced that patients who had received oral sucrosomial iron, featured a better post-surgery Hb level, which led to an abatement of RBC transfusions, to a quicker patient recovery, and ultimately to lower hospital-related costs.

In reference to the improved Hb status in our patients, Hb balance is a paramount issue: iron deficiency and anaemia are an extremely important aspect for post-operative patient outcome and have been demonstrated to be associated to poorer prognosis, increased LOS, slower functional recovery shorter walking distance test at discharge [5, 8, 34–36], and higher morbidity and mortality.

As underlined in a recent review by Munoz [8], iron deficiency should be treated in a timely manner by means of pre-operative iron supplementation, as post-operative iron does not accelerate the correction of anaemia or reduce RBC transfusion rate. Iron supplementation, however, should not be limited to anaemic patients alone, but extended also to non-anaemic patients undergoing a surgical procedure, since in the likely case of substantial blood loss, depleted iron stores might be insufficient for supporting rapid erythropoiesis needed for rapid recovery from surgery [5, 8].

The awareness of the role of iron supplementation in the orthopaedic surgery setting is gradually increasing and calls for further insight on modes of administration and formulations available.

Two recent studies have investigated pre-operative ferrous sulphate in major surgery. The study by Lidder [17] described the effect of ferrous sulphate 200 mg administered three times a day for two weeks before colorectal surgery against a control group with no iron supplementation. This led to a significant decrease in RBC transfusions and an overall healthcare cost saving of 66% [17]. The study by Andrews [11] on patients awaiting elective hip or knee replacement described supplementation with ferrous sulphate 200 mg twice-daily starting four weeks prior to surgery, which circumscribed immediate post-surgery fall in Hb concentration [11].

In our study, supplementation with sucrosomial iron started at least 4 weeks before surgery. Compared to patients who were not assigned to supplementation, patients who did receive oral sucrosomial iron showed a better post-operative Hb profile, proving oral sucrosomial iron supplementation to be effective in circumscribing post-operative fall in Hb in non-anaemic patients. The efficacy and safety of sucrosomial iron were previously investigated by a number of studies and confirmed in several disease settings such as chronic kidney disease and cancer, in both anaemic and non-anaemic patients [22–27, 37, 38].

So far, the potential of oral iron supplementation has been largely underestimated due to limitations such as gastrointestinal side effects (10–40%) and by low absorption rate (10–15%) typical of older oral iron formulations. A study by

Garrido-Martin et al. [38], published in 2012, compared the effect of intravenous and oral iron on peri-operative anaemia and RBC transfusion after cardiovascular surgery, concluding that the use of IV or oral iron supplementation was ineffective in correcting anaemia and reducing RBC transfusion requirements after cardiopulmonary by-pass [38]. However, the evaluation referred to an oral formulation of ferrous fumarate. More recently, a new oral formulation of sucrosomial iron has produced different results. Indeed, the study by Brilli et al. [22], comparing the bioavailability of oral sucrosomial iron to that of other oral iron formulations—such as ferrous sulphate, ferrous bysglicinate, ferrous fumarate, and a water-dispersible micronised ferric pyrophosphate and lecithin preparation—demonstrated a markedly higher efficacy for sucrosomial iron in replenishing ferritin stores over the other formulations [22, 27]. Therefore, the use of iron supplementation by oral administration and its potential should be reconsidered in light of this new evidence.

In general, in the case of surgical procedures, treatment of non-anaemic patients (with ferritin and Hb levels within normal range) with oral sucrosomial iron 30 mg/day, for at least three weeks, should limit the post-operative Hb drop. However, the dosage can be increased in the case of patients needing greater Hb and/or ferritin replenishment or in the case target Hb levels need to be reached within shorter time. The safety of higher doses of sucrosomial iron was reported in a recent study by Giordano [36] on patients with sideropenic anaemia, in whom the administration of 4 capsules/day produced an increase of 1.0 g/dl of Hb within a median time of nine days, with no increase in side effects.

From the point of view of optimal PBM, the use of sucrosomial iron in non-anaemic patients and its effects on post-operative Hb profile prevented the need for RBC transfusions in a large number of patients and allowed to achieve sufficiently adequate post-operative Hb levels for patients to progress more rapidly towards functional recovery, compared to patients who had not received iron supplementation. As evidenced by the head-to-head comparison for the subset of patients, RBC transfusions among (+ iron) patients were nil, and recovery was achieved 2.5 days earlier compared to the (− iron) group for the same year. Hence, although it may be argued that the decrease in RBC transfusions might reflect changes in clinical practice (e.g., improved screening, increasing awareness among physicians on the overuse of RBC transfusions and a tendency to withhold transfusion when not strictly necessary) [19], these figures from the head-to-head comparison for 2016 alone provide evidence of a relationship between iron supplementation and the improvements in the parameters observed.

From a cost point of view, considering the subset of patients analysed, these improvements translated into an expense reduction of 1763.25 €/patient. Thus, it appears certainly to be worth the upfront expenditure of € 20/patient for iron treatment with sucrosomial iron, especially in consideration of the overall benefits of patients' quality of life and a more efficient allocation of hospital staff and resources.

Indeed, considering that prosthetic joint replacement procedures are rapidly rising and that joint replacement absorbs a consistent portion of healthcare resources, such figures take on even further relevance. According to figures from Italian national registries [39], up to 160.000 arthoplasties (THAs) are performed in the country each year [39, 40]. A recent study by Jimenez-Garcia [41] on the trends of primary total hip THA in Spain from 2001 to 2008 evidences the significant increase in hospitalizations for THA—figures in line with trends for the USA and other countries and which are foreseen to soar by 174% in 2030 in the USA alone [41]; moreover, although the study by Jimenez-Garcia reports a significant decrease in LOS from 13 days in 2001 to 10.45 days in 2008, the cost per patient has dramatically increased by a 42.8% [41]. If on one hand such increase is largely explained by the increase in technology and costs of implants and surgical materials, on the other this is also caused by the greater risk profile and comorbidities of patients undergoing THA as well as post-surgical costs [41]. Hence, in such setting, the added value of addressing preventable issues, such as for example Hb status as foreseen in pillar 1 of PBM, is evident in view of both short- and long-term cost objectives [41, 42]. Results from our study demonstrate improved patient outcome both in terms of recovery of physiologic Hb levels and of functional recovery time by means of a simple preventive intervention of highly available sucrosomial iron administered three weeks prior to surgery.

Several studies have confirmed the effectiveness and high tolerability for oral sucrosomial iron. Results from the present study provide evidence of the effectiveness of oral sucrosomial iron in containing fall in post-operative Hb levels, decreasing RBC transfusion, LOS and, thus, cost-related expenses, while avoiding hypersensitivity reactions to IV infusion. Indirectly, this positively affects patient recovery, management of restrictive RBC transfusion policies, allows a better management of hospital resources, also providing a dramatic improvement of Hb on 30th day after surgery.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The present study was performed in accordance with the principles outlined in the Declaration of Helsinki. Being an initiative

of a pre-operative protocol standardisation established at the Orthopaedics Department, the study was presented to the local Ethics Committee of the Humanitas Research Hospital for approval and patients' clinical data were handled as agreed by patient's informed consent.

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