Title: **Intraoperative measurement of bone electrical potential: a piece in the puzzle of understanding fracture healing.**

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ABSTRACT

Introduction: Bone electrical potentials change with the force applied. Also, fracture alters the bone electrical potential, so it becomes more electronegative. These potentials have an important role in fracture healing, bone growth and remodelling. Literature data on the influence of fracture operative treatment on bone electrical potentials, and possible consequences of this influence, are extremely deficient. Objective of this study was to establish a method of intraoperative bone potential measurement, and to try to find a correlation between electrical potential and fracture type, osteosynthesis method and prognosis.

Patients and methods: 52 patients with a pertrochanteric fracture were included in the study. Bone electrical potentials were measured intraoperatively.

Results: Near the fracture site potentials of -199 up to -267 mV were recorded. Mean measured potential of bone plate after fixation was -240 mV. Bone potentials were correlated with the subtype of fracture and early mobilisation of patients.

Conclusions: Bone potentials, caused by fracture, can be measured intraoperatively; and operation procedure, as such, influences these. Measured potentials depend on the fracture type, and can be correlated with prognosis.

Introduction

The fact that the strain is associated with bone remodelling and healing has been known for more than 120 years. This process is closely related to the electrical field that is induced at the same time [1, 2]. Strain changes the electrical potential of bone: parts exposed to the compression force develop negative potential, and parts subjected to the tension force positive potential. Negative potential is associated with bone deposition, and positive with bone resorption [3-8].

Friedenberg and Brighton provided evidence that a vital long bone acts as a unity in producing electric potentials. In the typical electro-potential curve pattern of normal long bone, the metaphysis is negative with respect to the epiphysis, and the diaphysis is isopolar or electropositive. Metaphysis reaches a peak in electronegativity two to three centimetres below the epiphysis. In a fractured bone, the entire shaft becomes electronegative; the metaphyseal peak becomes more negative; and a secondary peak of electronegativity, that may exceed the metaphyseal peak, appears over the fracture site [9]. It is assumed that this potential has an important role in fracture healing. Numerous trials show the positive effect of electro stimulation on fracture healing, bone nonunions healing, and osseointegration of metal implants [10, 11]. Isaacson and Bloebaum provided an excellent overview of the successful application of electricity. Nevertheless, scepticism, due to the lack of homogeneity with trial design and dosage, still exist in scientific community [1].

Bone healing is an extremely complex process. Bone is one of the few tissues that can heal without scar formation. Bone healing, as such, recapitulates embryonic bone development. Despite the progress of knowledge of bone healing, there is still a high complication rate in the form of slower healing of fractures, non-unions and malunions [12, 13]. The role of the bone electrical potential, although disputed in some studies, should stay in

focus of the fracture healing research [14, 15]. More comprehensive understanding of the bone electrical potential, could improve fracture treatment. This is confirmed by some of the latest review articles in this field [1, 12, 16, 17]. Significant differences in potentials measured in dried, recently excised and living bone, confirm the value of the *in vivo* research, especially in humans [18].

Intraoperative measurement of bone electrical potential is a highly complex method, due to the spectrum of influential local and systemic factors. Therefore, data in literature are extremely deficient. To our knowledge, there are no published data on intraoperative electrical potential measurement of fractured bone, changes of potential during operation, and potentials of bone plates. Objective of this study was to 1) establish a method of intraoperative bone potential measurement, 2) establish a correlation between electrical potential and fracture type, osteosynthesis method and prognosis.

Patients and methods

All patients admitted to our department with pertrochanteric fracture in a six month period were planed to be included in the study. All included patients underwent fixation with DHS (dynamic hip screw). Operation was performed on extension table. Most of the patients underwent spinal anaesthesia, and some general anaesthesia. Type of anaesthesia was included as predictor variable in multiple linear regression.

Method for intraoperative measurement of the bone electrical potential should be simple and quick, not to compromise the safety of operation and duration; and, at the same time, precise enough to avoid parasitic potentials of surrounding tissues, especially muscles. In the first stage of this study the method of Friedenberg with a silk wick, soaked in saline

solution, isolated with plastic tube was used [9]. It proved to be difficult to apply in this experimental setting. Measured potential was not stable; it depended on surrounding tissue, haemostasis, amount of saline solution and probably other unrecognized parameters. Also, this method was time-consuming, and complicated, in operation setting. This method was used to map periostal and cortical potentials in operating field, and to choose the optimal measurement point for later method.

In the second stage, electrical potential was measured using a thin Kirschner wire introduced through bone cortex at the selected point and pointed to opposite cortex, not penetrating it. All Kirschner wires were of the same length (9 cm) and diameter (1.2 mm). First Kirscner (K1) wire was used for measuring potential near the fracture site. It was introduced 8cm distal to the tip of great trochanter in anterolateral to posteromedial direction, not to interfere with the site for DHS implantation. It had no contact with tissues other then bone. Other Kirscner wire (K2), used as a control probe, was introduced percutaneously into distal femur metaphysis two to three centimetres from epiphysis; and third (K3), also control probe, into proximal tibial metaphysis two to three centimetres from epiphysis. Kirschner wires were connected using clamps to multimeter (YF-78 Multimeter). Neutral electrode (inductive rubber) was placed behind ipsilateral gluteus. This method is similar to a method for measuring potentials and applying electro stimulation to pseudoarthroses, described by Friedenberg 15 years later [19]. Potentials were recorded immediately after introduction, prior to fracture reposition. Second measurement was done after satisfactory reposition, controlled with x-ray intensifier. Third measurement was done after fixation, prior to wound closure. At the same time potential of DHS plate was measured. Potential measured in this manner were arguably more stable and uniform.

Patients were divided into groups according to subtype of fracture (AO classification: 31-A1, 31-A2, 31-A3) [20]. Also, patients were divided into two groups depending on

successful mobilisation in early postoperative period. Publicly available R program for statistical analysis and the method of multiple linear regression were used [21]. Potential measured at K1 site was a dependant variable, and fracture subtype, age, sex, ASA (American Society of Anaesthesiologists) score and type of anaesthesia were predicting variables. Second analysis was done with early mobilisation as dependant variable, and fracture subtype, measured potentials, age, sex, ASA stage, type of anaesthesia as predicting variables. Paired t-test was used to compare intraoperative changes in electrical potentials. Difference in potentials between K1 and K3 site, was used as corrected K1 potential (please see discussion), and was also included in the analysis.

Results

Fifty-two patients (37 female and 15 male) were included. Mean age was 79.4 (range 62 -103 years) years. Average bone potentials are presented in Table 1. Differences in potentials at K1, K2 site and corrected K1 before, after reposition and after fixation were statistically significant ($p<0,001$).

Twenty patients with A1 fracture type, 23 with A2 fracture type, and 9 with A3 were included. Fracture type was significant predicting factor for measured potential, especially corrected K1. Potentials in patients with A1 and A2 fracture types are presented in Table 2 and Table 3. Reports of multivariate statistical analysis are presented in Table 4.

Twenty-two patients were successfully mobilised in early postoperative period, 30 patients were unable to walk. Potentials in patients mobilised early, and those that were not, are presented in Tables 5 and 6. Corrected K1 potential proved to be significant predicting

factor for early mobilisation, in multivariate analysis, including the fracture type as well. Results are presented in Table 7.

Discussion

Intraoperative bone electrical potentials in our study were relatively high comparing to other studies [3, 4, 9, 19, 22, 23]. This can be explained, namely this is an intraoperative study, performed on human subjects, in an acute period after injury.. Probe was placed near the fracture site, and it was placed bicorticaly. One other studies also described bone potentials as high as 300 mV [24].

Operative injury to surrounding tissues, especially muscles, periosteum, and bone could have bean a cause of bias [25]. It is hard to completely neutralize influence of age, sex, metabolic diseases, and other systemic factors that could cause additional bias. Idea of measuring potentials at distal femoral metaphysis and proximal tibial metaphysis, was to control these factors. Potential of the whole bone becomes more negative in fractures, especially in metaphyseal area. It was expected that bone potential measured at distal femoral metaphysis (K2 site) would be proportional to potential measured near fracture site [9]. It wasn't expected that a Kirschner wire placed in proximal tibia (K3 site) would signal potential changes due to the fracture of femur. Results of this study confirm aforementioned assumptions. Potentials at distal femoral metaphysis were comparable to potentials near the fracture site. Potentials at tibial metaphysis were significantly lower, and these did not follow changes near the fracture site during operation. Conclusion is that if the operation injury to tissues (and not the fracture as such) was the primary cause of measured potential, it would be expected that differences between K1 and K2 site (in average 35-40 cm apart) would have

been greater than those between K2 and K3 site (5-7cm apart). Since measurements have shown the opposite, conclusion is that potentials near the fracture site were caused by fracture.

Difference in potentials between K1 and K3 site was used to calculate corrected K1 potential, with idea to neutralize systemic factors that influence the bone potential. Strong correlation of potentials at K1 site, and corrected K1 potentials, with fracture type, can be partially explained by the selection of measurement point (8cm from the tip of greater trochanter). Actually, fracture line in more complex fractures, could have been closer to measuring point.

Undoubtedly osteosynthesis affects electric potentials of operated bone. This can be measured near the fracture site, but also at distal metaphysis. As a rule, bone potential becomes more electronegative after reposition and fixation. Based on previous research, assumption is that this change can have a positive effect on fracture healing. It should be noted that there were some exceptions to this rule, but too few to make a statistical analysis, and to explain its meaning. Further investigations are needed.

Correlation of electric potentials with early mobilisation can be disputed, since it primarily depends on patient general condition and fracture type. Nevertheless, potentials were recognized as significant predicting factor in multivariate analysis. Further investigations are needed.

There is one more aspect of the intraoperative bone potential research, and it is corrosion of metal implants. Potentials as high as measured in our study, can have an effect on corrosion of metal implants, in combination with fretting, local acidity, implant surface abrasions and other factors. Corroded metal implant can act as a battery, which makes this process even more complex. Corrosion of metal implants can interfere with osseointegration and bone healing; and can lead to implant failure [26, 27].

Limitations in the study were relatively small number of patients, short follow-up period and a measurement limited to pertrochanteric fractures.

Controversies still exist in understanding the role of electrical potentials in bone growth, remodelling, and fracture healing. These controversies complicate clinical application of bone electrical stimulation, despite numerous studies that confirm the positive effect. One of the main objections is a question of dosage, so the research on bone electrical potential is still current [1, 17]. Results from this study may help to clarify this issue. It is very difficult to measure electrical field strengths inside living organisms *in vivo*, nevertheless, this research could provide valuable information for understanding bone healing [25, 28]. It can be the basis for future research, with objective to anticipate the prognosis of fracture, to assess the quality of osteosynthesis, to improve osteosynthesis and electro-stimulation methods, and to avoid corrosion problems.

Conclusions

Our results show that it is possible to measure bone potentials, caused by fracture, intraoperatively; and that operation procedure, as such, influences these. These potentials depend on the fracture type, and can be correlated with prognosis, with the idea to anticipate treatment failure. Results shown can be useful for optimizing electrotherapy of fractures, nonunions and implant osseointegration. This study creates an opportunity for further research that could clarify the role of electricity in bone growth, remodelling and fracture healing.

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Table 1

Average potentials measured in the entire study group (mV).

	Before reposition	After reposition	After fixation
K1 site	-199	-240	-241
K2 site	-183	-180	-154
K3 site	-125	-118	-116
Corrected K1	-74	-122	-125
		Plate potential	-240

Table 2

Potentials measured in patients with 31-A1 fracture type (mV).

	Before reposition	After reposition	After fixation
K1 site	-162	-210	-212
K2 site	-148	-147	-130
K3 site	-110	-112	-109
Corrected K1	-52	-99	-103
		Plate potential	-211

Table 3

Potentials measured in patients with 31-A2 fracture type (mV).

	Before reposition	After reposition	After fixation
K1 site	-220	-261	-265
K2 site	-202	-192	-171
K3 site	-133	-127	-121
Corrected K1	-87	-134	-144
		Plate potential	-273

Table 4

Results of multiple linear regression with corrected K1 potential as a dependant factor; and fracture type, age, sex, ASA score and type of anaesthesia as predictors.

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Fracture type	2	48655	24327.4	57.2746	4.287e-13 ***
age	1	890	890.1	2.0957	0.1546
sex	1	166	166.3	0.3914	0.5347
ASA score	1	24	24.2	0.0571	0.8122
Anesthesia	1	475	475.4	1.1191	0.2958

Table 5

Potentials measured in early mobilised group (mV).

	Before reposition	After reposition	After fixation
K1 site	-176	-215	-220
K2 site	-160	-161	-131
K3 site	-110	-112	-108
Corrected K1	-66	-103	-112
		Plate potential	-219

Table 6

Potentials measured in non-mobilised group (mV).

	Before reposition	After reposition	After fixation
K1 site	-215	-257	-267
K2 site	-199	-198	-170
K3 site	-129	-121	-119
Corrected K1	-86	-135	-148
		Plate potential	-255

Table 7

Results of multiple linear regression with early mobility as a dependant factor; and corrected K1 potential, fracture type, age, sex, ASA score and type of anesthesia as predictors.

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Corrected K1	1	2.7031	2.70307	21.2235	3.49e-05 ***
Fracture type	2	0.2677	0.13386	1.0510	0.3582010
age	1	1.8634	1.86343	14.6309	0.0004087 ***
sex	1	0.0237	0.02375	0.1865	0.6679868
ASA score	1	0.8826	0.88263	6.9301	0.0116470 *
Anesthesia	1	1.3478	1.34779	10.5824	0.0021964 **