 Acta Chir Orthop Traumatol Cech. 87, 2020, No. 1
p. 9–16

ORIGINAL PAPER
PŮVODNÍ PRÁCE

Creatine Kinase and Myoglobin Levels as Indicators of Perioperative Muscle Damage during Open- and Mini-Invasive Stabilization of Thoracic and Lumbar Spine Fracture – a Prospective Randomized Study

Hladiny kreatinkinázy a myoglobinu jako indikátory perioperačního poškození svalů při otevřené a miniinvazivní stabilizaci zlomeniny hrudní a bederní páteře – prospektivní randomizovaná studie

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ABSTRACT

PURPOSE OF THE STUDY

In this randomized prospective study, we monitored and compared perioperative changes in skeletal muscle enzymes blood levels in open and mini-invasive stabilization of thoracolumbar spine fractures. The established hypothesis was to confirm higher blood levels of muscle enzymes in open stabilization.

MATERIAL AND METHODS

This study included 38 patients with the mean age of 46.4 years. 19 injuries were managed in an open procedure and 19 procedures were mini-invasive. Venous blood was taken intermittently at short intervals to determine the levels of skeletal muscle enzymes. The catalytic concentration of creatine kinase was determined via an enzymatic UV-test, and the concentration of myoglobin via electro-chemiluminescent immunoassay. Enzyme levels were processed statistically. The Wilcoxon test was used.

RESULTS

The median increase in the values of both enzymes is higher in the mini-invasive method than in the open method in both the surgery phase for the injury and in the extraction phase. The median increase in the values of both enzymes is higher in both methods for the primary procedure phase compared to the extraction phase. All results are statistically significant at p of <0.05. All tests were calculated using the MATLAB Statistics Toolbox.

DISCUSSION

A very surprising finding, when testing the hypothesis of the levels increasing mainly in open stabilization, was confirming the opposite. Both enzymes were higher in the mini-invasive approach to stabilising the spine after the injury, but also after the extraction. This contradicts the available literature. However, this can be explained by the methodology of enzyme levels determination in the previously published studies.

We believe that this phenomenon can be partially caused by an iatrogenic mini-compartment of muscles in the postoperative period, absence of wound drainage, but also by higher muscle contusion when inserting bolts through the tubes via small incisions, when the tubes penetrate to the entry points relatively violently and the muscles in this area are affected more than in the classical skeletization.

CONCLUSIONS

Analysis of biochemical changes in open and mini-invasive surgery did not confirm the hypothesis that levels of creatine kinase and myoglobin enzymes increase especially in open stabilization. On the contrary, they were statistically significantly higher in mini-invasive procedures.

Key words: creatine kinase, myoglobin, muscle enzymes, spine fracture, spine surgery, miniinvasive surgery.

This study was performed with the support of the grant GAUK (Charles University Grant Agency) No. 764214.

INTRODUCTION

Minimally invasive methods of spine surgery are becoming ever more popular and widespread (6, 13). One of the factors is the impression of minor injury to the muscular corset of the spine. The classic, open method (OPEN) reaches the spine via skeletization, pulling the muscle wall to the sides. In the mini-invasive method (MIS), the implant is introduced percutaneously from mini-incisions using special instrumentation. Both methods have their advantages and disadvantages (10). The classic method leads to greater blood loss and higher postoperative pain. Even strict subperiosteal skeletization, which is not always possible, is associated with muscular denervation, decreased vascular supply, and contusions caused by retractors and inserted screws, resulting in long-term changes in muscle structure. Minimally invasive high-quality posterolateral fusion is not feasible, fractures are more difficult to reduce but there should be no chronic muscle damage, the learning curve is longer than in the conventional method and surgery is more demanding on technique and time. However, instrument tubes can cause local muscle contusion at the insertion site. Open fracture stabilization damages the muscles more in long-term follow-up. Both methods are certainly associated with more or less perioperative muscle damage, which can be objectively verified based on the changed levels of skeletal muscle enzymes. The most prominent enzymes are creatine kinase and myoglobin.

Creatine kinase (CK) is important for the energetic metabolism of the muscle – creatine phosphate serves as a standby supply of muscle energy.

Myoglobin (MYO) binds the oxygen in the muscle and thus provides the essential oxygen supply for the beginning of muscle work. After muscle injury it is released and can be detected in blood serum. The causes of this finding are identical with the increases in creatine kinase activity but there is a difference especially in the dynamics. Myoglobin is released from the muscles earlier and, on the contrary, persists in the blood for a shorter period of time than CK.

Objective

In this randomized prospective study approved by the local Ethics Committee we monitored and compared perioperative changes in the levels of these enzymes in the classical, i.e. open and mini-invasive stabilization of fractures of the thoracolumbar spine. The established hypothesis was to confirm higher levels of muscle enzymes in the classical, i.e. open stabilization.

MATERIAL AND METHODS

Patients with a type A and B thoracolumbar vertebral fracture according to the Vaccaro's classification (14) without neurological injury and without any other associated injury to avoid an eventual effect on the level of enzymes were consecutively recruited for this prospective randomized study. A total of 38 injured patients (27 type A and 11 type B fractures, with the mean age of 46.4 years (18–68) were included in the study. Of these, 28 were men and 10 women. The mean age was 47.8 in men and 42.7 in women. 19 injuries were managed in an open procedure and 19 procedures were mini-invasive.

A CT and MRI scan was performed, the indication of the surgery was determined and an informed consent with participation in the study was acquired. The patient was randomized to the stabilization method using random number generator. The USS Fracture (DePuy-Synthes, Switzerland) implant was used for the open method of stabilization and the USS Fracture MIS (DePuy-Synthes, Switzerland) was used for the mini-invasive procedure.

Four mililitres of venous blood to determine the levels of skeletal muscle enzymes were collected intermittently 1 hour prior to the surgery as a standard baseline value, 1 hour after the surgery, and then on the day of the procedure in 4 samplings every 6 hours, the next day in 3 samplings every 8 hours, followed by 2 samplings every 12 hours and afterwards once a day until the values normalized or the patient was discharged. In total, we received at least 16 blood samples from each patient in the primary surgery due to the injury, allowing us to determine the levels of skeletal enzymes after the surgery.

The catalytic concentration of creatine kinase (CK, EC 2.7.3.2) was determined via an enzymatic UV-test, and the concentration of myoglobin via electro-chemiluminescent immunoassay (ECLIA). Roche Diagnostics sets were used for both analytes; the Cobas 8000 analyser system was used for the measurements – creatine kinase on module c702, myoglobin on module e602 by Roche Diagnostics (Basel, Switzerland).

Surgery

All operations were performed by skilled spine surgeon within 24 hours after trauma. All the patients were operated on the next day after injury at 8 am. Primary surgeries due to the injury, means stabilization (ST), were performed in the prone position with a carefully supported body to avoid pressure on high-risk areas (spines) and on the muscle corset, which could affect the level of muscle enzymes. Two segments were fixed in all patients in both methods. In open stabilization, we approached the spine via a medial longitudinal incision above the spinal processes of vertebrae managed with instruments and the injured vertebra, protecting the supra- and inter-spinous ligaments. The muscles were carefully dissected and pulled out laterally in the best feasible and sub-periostal way, and two retractors were used to maintain their position. Screws were introduced under the control of one fluoroscopic device in the lateral projection and, after introduction, they were also checked in the postero-anterior projection. After the instrumentation was completed, the sutures of the muscular fascia and the muscles to the spinous processes, the subcutaneous tissue and the skin were performed. The wound was drained using two vacuum drains. In the mini-invasive method, 4 longitudinal skin sections, about

2 cm long, were made about 3 cm from the median line. Instruments were used for blunt penetration to the entry points for mini-invasive stabilization, for the insertion of the bolts; the control was performed using two fluoroscopic devices simultaneously in the lateral and postero-anterior projection. After the insertion of the screws, connectors were inserted and rods tunnelled through muscles and fixed to the connectors. Every step was performed through instrumentation tubes. These small incisions were not drained and subcutaneous tissue and skin sutures were performed. On the first day, the patients were monitored at an intensive care unit and were mobilized the next day after a transfer to the standard ward. The blood loss was measured and Visual Analog Scale for pain monitoring was used.

During implant extraction (EX), which was indicated at the earliest 12 months after the primary stabilization due to the injury, we proceeded in a similar way in both methods, i.e. careful and gentle skeletization in the open method and percutaneous extraction in the mini-invasive method. It should be noted here that the extraction of mini-invasively introduced material is surprisingly difficult and demands on the surgeon are greater than when removing a classically introduced implant. Also, there was a greater intensity of contusion in the muscles around the screws and connectors at the incision sites.

When removing the implants, we collected blood samples again to examine CK and MYO levels, but now at less frequent intervals. Samples were collected 1 hour before the surgery, 1 hour after and then 3 times every 8 hours. Afterwards, 2 samplings were performed every 12 hours and then once a day until the discharge or the stabilization of the levels. In total, at least 8 blood samples were obtained from each patient at the extraction.

Statistical methods

The Wilcoxon's test (equivalent to Mann-Whitney test) was used because variables did not follow a normal distribution; p-values ≤ 0.05 were considered statistically significant. All computations were performed with MATLAB Statistics Toolbox.

1) The increase in the concentration values of CK and MYO enzymes in the blood after primary procedure due to the injury, i.e. in ST was compared with the increase in the concentrations of these enzymes after the EX, for the MIS method and for the OPEN method.

2) The increase in the concentration of CK and MYO enzymes in the blood after MIS ST was compared with the increase in the concentration of these enzymes after OPEN ST.

3) The increase in the concentration of CK and MYO enzymes in the blood after MIS EX was compared with the increase in the concentration of these enzymes after OPEN EX.

The increase in the values was calculated separately for each patient, as the difference between the maximum concentration of the given enzyme during the measurement (i.e. the difference between the maximum value of all ST and EX samples, respectively, and the preoperative value measured before ST or EX, respectively).

In ST, we obtained the values for both enzymes in all 38 patients in the full extent. In EX, we obtained a full number of samples in 16 patients after open stabilization and in 16 patients after mini-invasive stabilization.

Let MAX-1_ST_CK_MIS represents for each participant the difference between the maximal value of CK measured during the stabilization MIS stage and the value of EX measured one hour before the MIS stabilization.

Analogously, MAX-1_EX_ CK_MIS is the difference between the maximal value of CK measured during the extraction MIS stage and the value of CK measured one hour before the MIS extraction,

MAX-1_ST_ CK_OPEN is the difference between the maximal value of CK measured during the stabilization OPEN stage and the value of CK measured one hour before the OPEN stabilization, and

MAX-1_EX_ CK_OPEN is the difference between the maximal value of CK measured during the extraction OPEN stage and the value of CK measured one hour before the OPEN extraction.

Analogous notation is used for myoglobin (MYO):
MAX-1_ST_MYO_MIS
MAX-1_EX_ MYO_MIS
MAX-1_ST_ MYO_OPEN
MAX-1_EX_ MYO_OPEN

The Visual Analogue Scale (VAS) was measured before operation (means after injury), 12, 24, 48 hours and 7 days after procedure always before analgetics administration.

Ethics

For this study the approval was given by our local institutional review board (IRB) and informed consent was obtained from each patient. The patients and their families were informed that data from the case would be submitted for publication, and gave their consent.

RESULTS

Statistical analysis

The medians of the following variables were compared:

MAX-1_ST_CK_MIS versus MAX-1_ST_CK_OPEN: p = 0.0000079777
MAX-1_EX_CK_MIS versus MAX-1_EX_CK_OPEN: p = 0.0132765068
MAX-1_ST_CK_MIS versus MAX-1_EX_CK_MIS: p = 0.0000192028
MAX-1_ST_CK_OPEN versus MAX-1_EX_CK_OPEN: p = 0.0013385815

MAX-1_ST_MYO_MIS versus MAX-1_ST_MYO_OPEN: p = 0.0000229623
MAX-1_EX_MYO_MIS versus MAX-1_EX_MY_OPEN: p = 0.0070684733
MAX-1_ST_MYO_MIS versus MAX-1_EX_MYO_MIS: p = 0.0000192028
MAX-1_ST_MYO_OPEN versus MAX-1_EX_MYO_OPEN: p = 0.0002268521

Table 1. Perioperative blood levels (μkat/l) of CK in primary stabilization procedure in MIS and OPEN procedures

Day	Sequence of sample	ST_CK mean MIS (μkat/l)	ST_CK mean OPEN (μkat/l)
1	1 preop	3.48	4.79
1	2	8.11	7.00
1	3	15.87	10.41
1	4	22.01	12.30
1	5	25.37	13.06
2	6	28.68	12.70
2	7	29.95	11.40
2	8	26.75	10.03
3	9	26.08	8.63
3	10	23.39	7.04
4	11	17.24	6.18
4	12	16.45	5.25
5	13	11.11	4.02
6	14	11.36	4.01
7	15	8.89	4.04
8	16	5.80	4.22

Table 2. Perioperative blood levels (μkat/l) of CK in implant extraction procedure in MIS and OPEN procedures

Day	Sequence of sample	EX_CK mean MIS (μkat/l)	EX_CK mean OPEN (μkat/l)
1	1 preop	1.1	1.7
1	2	3.4	3.7
1	3	7.0	4.9
1	4	7.8	5.1
2	5	6.9	4.9
2	6	6.1	4.3
3	7	5.4	3.4
4	8	4.5	2.8

The maximal concentration was reached in all patients at the following intervals:

ST CK MIS between samplings 3 to 10 (Table 1, Graph 1)

ST CK OPEN between samplings 4 to 7 (Table 1, Graph 1)

EX CK MIS between samplings 3 to 4 (Table 2, Graph 2)

EX CK OPEN between samplings 3 to 5 (Table 2, Graph 2)

ST MYO MIS between samplings 3 to 4 (Table 3, Graph 3)

ST MYO OPEN between samplings 2 to 5 (Table 3, Graph 3)

EX MYO MIS always in sampling 2 (Table 4, Graph 4)

EX MYO OPEN always in sampling 2 (Table 4, Graph 4)

Table 3. Perioperative blood levels (μg/l) of MYO in primary stabilization procedure in MIS and OPEN procedures.

Day	Sequence of sample	ST_MYO mean MIS (μg/l)	ST_MYO mean OPEN (μg/l)
1	1 preop	43.91	51.79
1	2	602.68	438.77
1	3	756.36	358.46
1	4	728.51	270.68
1	5	594.78	211.84
2	6	461.93	176.30
2	7	365.80	145.32
2	8	250.70	109.30
3	9	192.20	102.91
3	10	148.97	79.54
4	11	115.99	67.67
4	12	90.32	65.16
5	13	71.99	62.02
6	14	66.49	72.46
7	15	60.64	76.76
8	16	63.17	82.18

Table 4. Perioperative blood levels (μg/l) of MYO in implant extraction procedure in MIS and OPEN procedures.

Day	Sequence of sample	EX_MYO mean MIS (μg/l)	EX_MYO mean OPEN (μg/l)
1	1 preop	30.0	43.1
1	2	358.6	240.8
1	3	215.8	133.2
1	4	156.0	94.2
2	5	107.1	75.6
2	6	66.8	57.6
3	7	50.6	47.1
4	8	37.1	35.1

Results of the statistical analysis

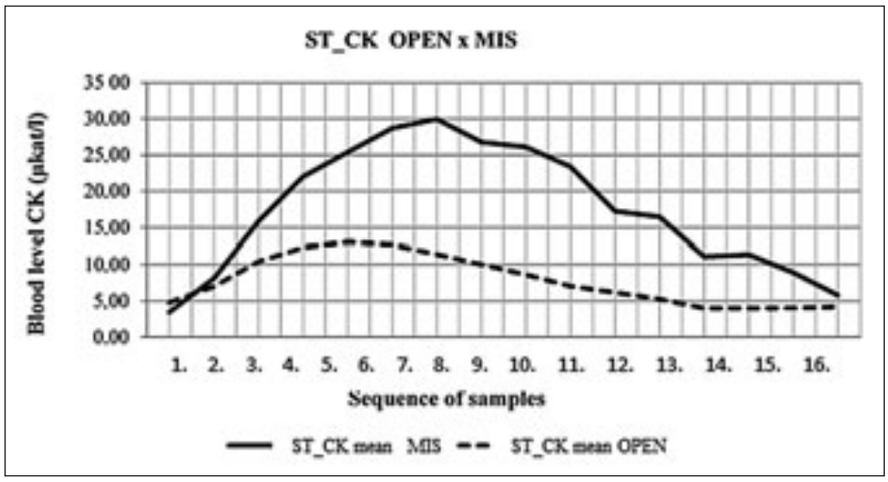
The increase in the values (more precisely the median increase in the values) of both enzymes (CK and MYO) is higher in MIS than in the OPEN method, both in the stabilization phase and in the extraction phase.

The increase in the values (more precisely, the median increase in the values) of both enzymes (CK and MYO) is higher in ST than in EX for both methods (MIS and OPEN). (Graphs 5, 6).

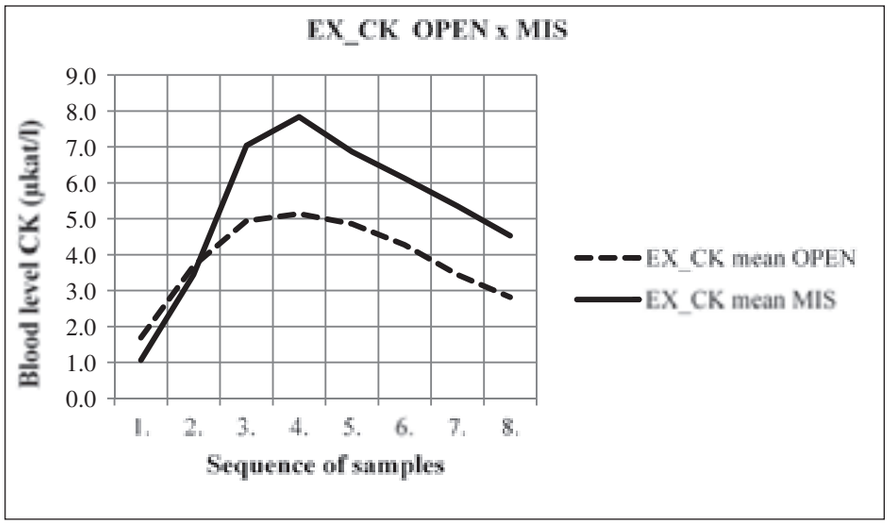
All results are statistically significant at p of < 0.05. All tests were calculated using the MATLAB Statistics Toolbox. The intensity of pain was higher in OPEN within day 1–3 and balanced in the day 7. (Graph 7).

The peroperative blood loss was in the OPEN 307 ml (80–720 ml) and postoperative 375 ml (200–610 ml) from drains. The values in MIS were 21 ml (10–55 ml) and postoperative were not measurable because of no drains were used.

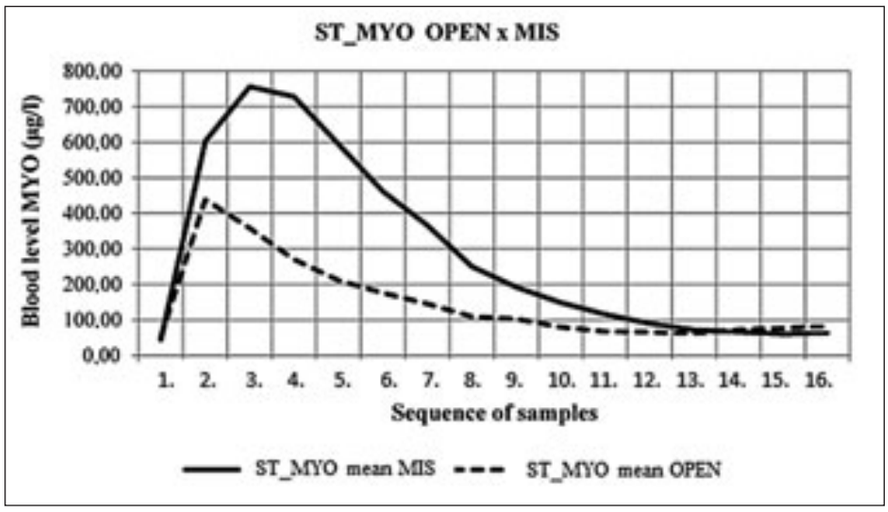
Graph 1. Perioperative blood levels of CK (μkat/l) in primary stabilization procedure in MIS and OPEN procedures. Detailed sequence and values of samples are in tables



Graph 2. Perioperative blood levels of CK (μkat/l) in implant extraction procedure in MIS and OPEN procedures. Detailed sequence and values of samples are in tables



Graph 3. Perioperative blood levels of MYO (μg/l) in primary stabilization procedure in MIS and OPEN procedures. Detailed sequence and values of samples are in tables



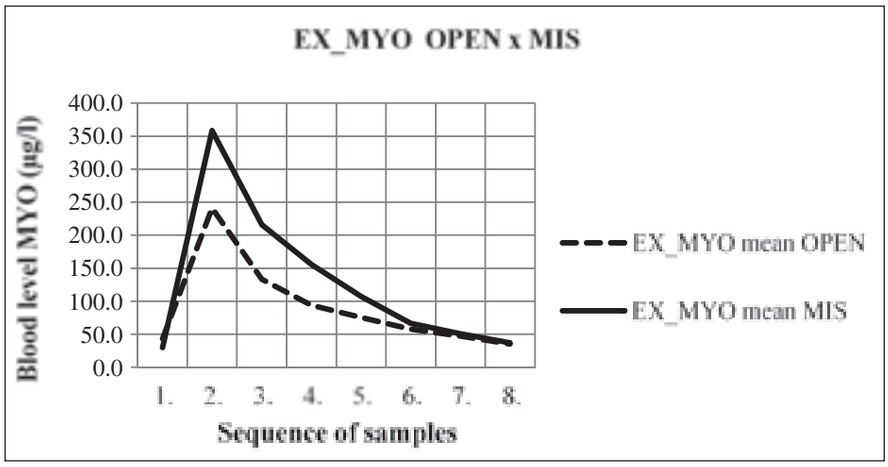
DISCUSSION

Given the above-mentioned characteristics and behaviour of both enzymes in the blood, when creatine kinase is released into the blood more slowly and is also excreted more slowly, whereas myoglobin is released and excreted more rapidly, both groups (open and mini-invasive stabilization) showed an increase in the MYO level with the peak already on the day of the surgery (day 1); the level began to decrease already 24 hours after the surgery, both in the primary procedure and extraction. CK level increased more slowly and culminated on the following day after the surgery (day 2), for both types of surgical approaches, and for both primoimplantation and extraction. MYO levels stabilized at the baseline preoperative value on the 4th postoperative day in the surgery due to the injury, and CK levels on the 6th postoperative day. After the extraction, MYO levels stabilized on the 4th postoperative day, but CK levels were still several times higher than the upper limit of norm at this time.

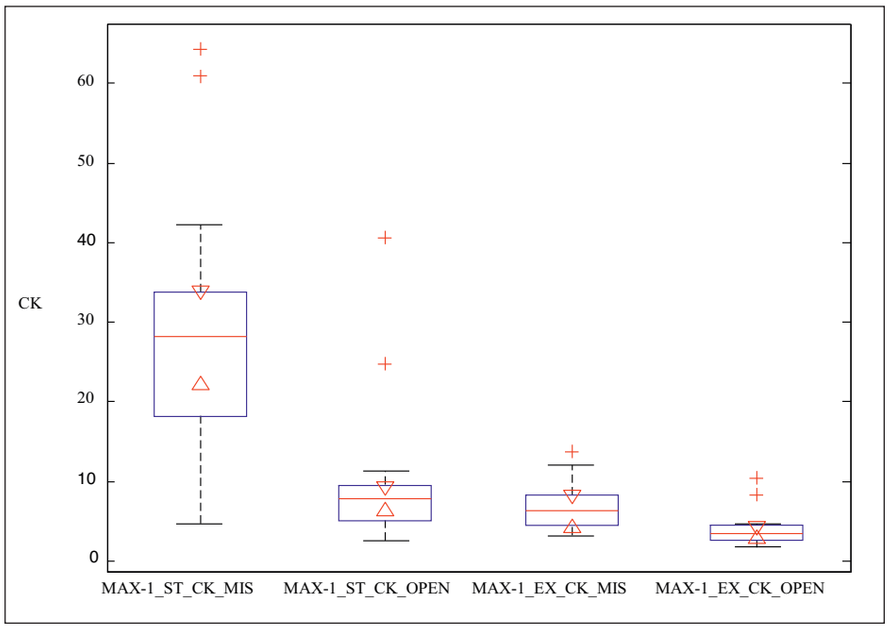
A very surprising finding, when testing the hypothesis of the levels increasing mainly in open stabilization, was confirming the opposite. Both enzymes were higher in the mini-invasive approach to stabilising the spine after the injury, but also after the extraction.

This contradicts the available literature. However, this can be explained by the methodology of enzyme levels determination in the previously published studies. Linzer compared the miniPLIF and the openPLIF surgery and took the samples one day before the surgery and on the postoperative days 1, 3 and 7 (9). He found higher myoglobin levels in openPLIF

Graph 4. Perioperative blood levels of MYO (µg/l) in implant extraction procedure in MIS and OPEN procedures. Detailed sequence and values of samples are in tables



Graph 5. Box plot of levels of CK (µkat/l) in ST an EX in MIS and OPEN surgery

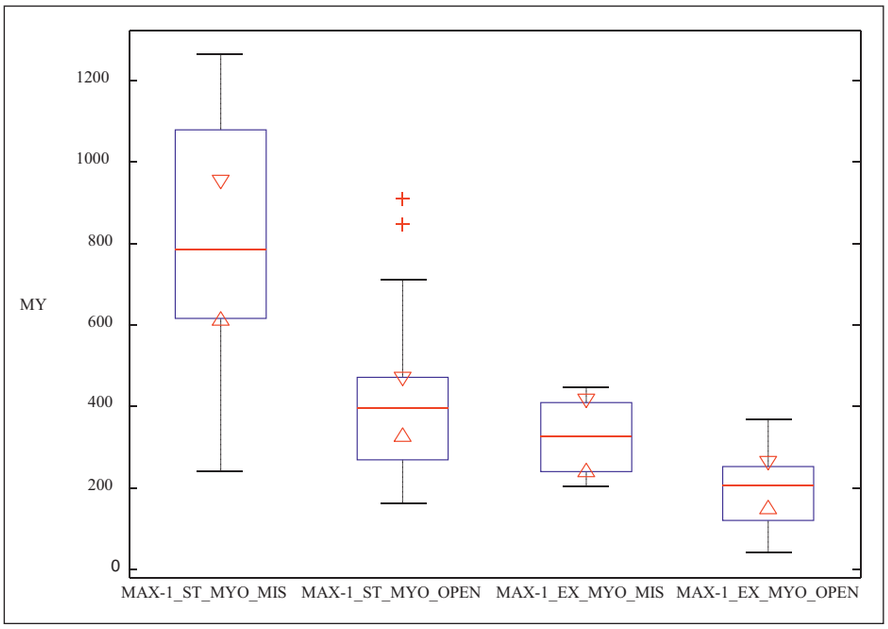


(464.4 ug/l) compared to miniPLIF (369.2 µg/l) on the postoperative day 1. Already on the postoperative day 3, the levels returned to the baseline. Similarly, CK levels increased on the postoperative day 1 in openPLIF to 24.5 ukat/l and 22.4 µkat/l for miniPLIF, respectively. Higher CK levels remained until day 3; on day 7, they were already normal. In a group of 6 men and 6 women after open surgery on the lumbar spine, Kumbhare evaluated CK levels at the intervals before the surgery, just after the surgery, then 6, 12 hours after the surgery, the next morning, and on the postoperative days 2, 4 and 6 (8). As in other studies, CK levels increased on the day after the surgery to the highest values and persisted for 2 to 4 days, decreasing more rapidly in women who did not achieve the levels of men. Waschke measured CK and MYO levels during open-label lumbar surgeries at long intervals (before surgery, day 2 after the surgery and the day of discharge) and found that the highest level was measured on the postoperative day 2 for both enzymes (15). Here, we believe that the existence of only 3 time-points for enzyme levels, degrades the study. Arts compared CK levels in only 2 samples in classical microdiscectomy and endoscopic discectomy, and found virtually the same CK elevation on the post-operative day 1 for both groups when compared with the preoperative level (2). Kawaguchi compared CK levels (in the intervals: before the surgery and 1, 3, 7, 14 and 21 days after the surgery) in the anterior and posterior procedures in the spine and found an increase in blood levels between days 1 and 3 after the surgery, with the return of the levels to the norm on the postoperative day 7 (4). The levels were significantly higher for posterior open approaches than for the anterior approaches. Adogwa monitored only CK levels in miniTLIF and openTLIF, and enzyme detection time-points were the day before the surgery and then on the days 1, 7 and weeks 6, 12, and 24 (1). Similarly to our study, there was an increase of CK levels in miniTLIF (628.07 U/L) as opposed to openTLIF (291.42 U/L) on the postoperative day 1. On day 7, the values were comparable. Unfortunately, he did not monitor myoglobin levels. He explains this phenomenon by iatrogenic postoperative compartment syndrome resulting from the absence of wound drainage in mini-invasive surgery, increased swelling and pressure in the paraspinal muscles and thus increased CK levels. However, he notes that this increase did not affect the final results.

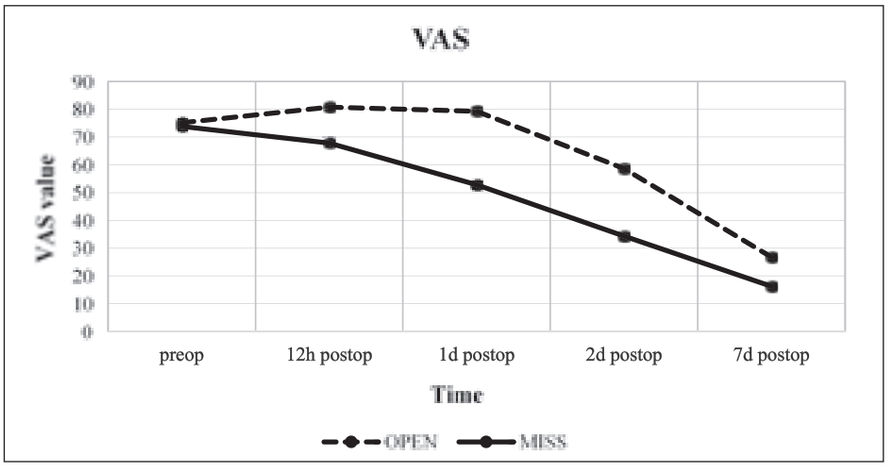
Taking into account that only a few studies compared classical open-ended methods of stabilization and mini-invasive introduction of virtually the same implant, and that most studies (3, 5, 7, 11, 12) only detected changes in CK levels, and that the sampling intervals were too long relatively to the metabolic activity of the enzymes, we can say that our study disproved the primary hypothesis thanks to the methods. We have rebutted the presumption that skeletal muscle enzymes will increase more in open procedures. Similar results, but only in

CK, were published by Adogwa (1). Our study confirmed his finding also with the behaviour of another of the enzymes – myoglobin. In agreement with Adogwa, we believe that this phenomenon can be partially caused by an iatrogenic mini-compartment of muscles in the postoperative period, absence of wound drainage, but also by higher muscle contusion when inserting bolts through the tubes via small incisions, when the tubes penetrate to the entry points relatively violently and the muscles in this area are affected more than in the classical skeletization. However, this only applies to the perioperative period. Muscle damage at MIS procedures is local in the point of screw insertion, while the OPEN procedures affect the entire range of skeletization. A higher extent of changes in OPEN surgeries can be expected in long-term monitoring of muscle corset damage, which will be the focus of further studies. We have confirmed the Loibl's finding that the blood loss and pain intensity is higher in OPEN surgery than in the MIS one (10).

Graph 6. Box plot of levels of MYO (μg/l) in primary procedure an implant extraction procedure in MIS and OPEN surgery



Graph 7. Visual analogue scale in postoperative period in stabilisation surgery in MIS and OPEN surgery



CONCLUSIONS

Analysis of biochemical changes in open and mini-invasive surgery to stabilize fracture of the thoracolumbar spine did not confirm the hypothesis that the levels of CK and MYO increase especially in open stabilization. On the contrary, they were statistically significantly higher in mini-invasive procedures, both at the primary procedure for the injury and the extraction of the implant.

ACKNOWLEDGEMENT
We would like to thank prof. ing. Luděk Müller, Ph.D., from the University of West Bohemia for elaboration the complete statistical data analyses.

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