



Validity of creatine kinase as an indicator of muscle injury in spine surgery and its relation with postoperative pain

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Purpose : to confirm the validity of postoperative creatine kinase (CK) values as an indicator of muscle lesion, assess the relationship of CK with variables indicating surgical invasiveness and investigate an association between CK values and excessive postoperative pain.

Material and Method : The study included 96 patients (mean age 62.8 years) who underwent instrumented spine fusion for degenerative lumbosacral disease. Serum CK concentration was determined on the first postoperative day. All patients received intravenous paracetamol and metamizole, and in cases of intense pain, rescue analgesia with iv meperidine. Patients were categorized according to whether or not they required rescue analgesia. Data on the number of levels fused, the duration of surgery, and operative bleeding were recorded in each patient.

Results : CK values were higher in men and in younger patients. Significant correlations were found between CK and the number of fused levels and duration of surgery. Only 17.7% of patients required rescue analgesia. CK levels did not significantly differ between patients who did not need rescue analgesia (1135 IU/L) and those who did (1421.5 IU/L).

Conclusion : Serum CK concentration is a valid marker of surgical muscle injury and is affected by the age and sex. Factors such as the magnitude and duration of surgery show a relationship with postoperative CK values. The incidence of severe postoperative pain is not significantly related to CK level.

Keywords : creatine kinase ; muscle ; pain ; spine fusion ; analgesia.

INTRODUCTION

The changes occurring in the paraspinal musculature following spine surgery have been related to the degree of postoperative pain (5,23). Serum creatine kinase (CK) level in the immediate postoperative period has been considered a suitable parameter for estimating muscle injury in various spinal procedures (1). CK level significantly correlates with the length and depth of the surgical dissection (13), and a significant relationship has been found between serum values of this enzyme and the duration and intensity of the pressure on paraspinal muscles exerted by retraction (1,9,16).

Hence, it would be reasonable to assume that there should be a relationship between CK values and postoperative pain. Several authors have reported an association between postoperative CK level and pain intensity in the immediate postoperative period (22) and at middle term (2,27). However, the

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published series only include procedures that are not highly invasive, such as microdiscectomy or simple decompression surgery. This relationship has not been investigated in cases of decompression with instrumented vertebral fusion, in which study of the association between muscle injury and the intensity of immediate postoperative pain would seem essential. The degree of pain immediately after a surgical procedure is a crucial part of the sequence in the following line of reasoning : smaller incision -less tissue injury -less postoperative pain -shorter hospital stay -better final outcome. This perspective forms the theoretical basis of the minimally invasive surgery approach that is now so much in vogue.

The aims of this study are to confirm the validity of CK values as indicative of muscle lesion in lumbar spine surgery by analyzing the relationship of this parameter with variables indicating surgical invasiveness (eg, operating time and number of fused segments), and to investigate the relationship between serum CK values and the presence of excessive postoperative pain in patients receiving a decompression plus instrumented vertebral fusion through a midline approach.

MATERIAL AND METHOD

This is a retrospective study including patients surgically treated for their back condition during the period of 2007 to 2010 in a second-level hospital. Patients were older than 18 years and had degenerative lumbar spine disease scheduled for surgical treatment. Patients with tumors, infectious disease, or traumatic injury of the spine, and those with abnormal hepatic function were excluded. In all cases, the procedure involved posterior midline incision ; paravertebral musculature was detached from vertebral arches and retracted laterally ; then an instrumented fusion and, when it was considered indicated, a decompressive maneuver was performed. For each patient, we collected demographic (age, sex) and anthropometric (weight, height, and BMI) data, comorbidities (diabetes and depressive syndrome), surgery-related data (operating time, number of fused levels), and duration of hospitalization.

At completion of surgery in our center, patients are taken to the recovery area where they remain for approximately 5 hours, and are then transferred to the hospital ward. All patients received analgesic treatment according to our established protocol, consisting of intravenous

administration of metamizole 2 g/6 hours and paracetamol 1 g/6 hours. Patients who experienced intolerable pain were given a 100-mg subcutaneous dose of meperidine as rescue analgesia. If pain control was not achieved, the dose could be repeated every 8 hours. The decision to administer meperidine was at the discretion of the attending nurses, based on their clinical judgment regarding the intensity of pain. Patients were divided into two groups according to whether they had required rescue analgesia (extra-pain group) or not (regular-pain group), and the number of analgesia doses needed by each patient in the first 72 hours was recorded.

At 24 hours following the intervention, serum CK levels were determined (N-acetyl cysteine activated CK activity monitored on a Siemens Dimension EXL [Siemens AG, Erlangen, Germany] ; Normal values 32-294 IU/L for men and 33-211 IU/L for women). C-reactive protein (CRP) concentrations were also recorded (Turbidimetric immunoassay Siemens Dimension EXL [Siemens AG, Erlangen, Germany] ; Normal values : 0, 5-3 mg/L).

The variable *CK serum levels* underwent logarithmic transformation to obtain a normal distribution. Statistical analyses included a *t* test to analyze differences between two mean values and one-way ANOVA to compare three or more groups. The chi-square test was used to compare percentages. For the correlation analyses, Pearson's coefficient was determined. Significance was set at $p < 0.05$.

RESULTS

The study included 96 patients (55 women and 41 men) with a mean age of 62.8 years. The diagnoses leading to surgery were spinal stenosis in 57 cases (59.3%), degenerative disc disease in 17 cases (17.7%), isthmic spondylolisthesis in 12 cases (12.5%), and degenerative lumbar scoliosis in 10 cases (10.4%). The patients' descriptive data are shown in Table I ; 13.5% had diabetes and 31.2% depressive syndrome. A mean of 1.9 vertebral segments were fused (range 1 to 9), including one segment in 47.9% of cases, two segments in 34.4%, three segments in 5.2% and more than three segments in 12.4%. The mean CK value at one day following surgery was 1185.8 IU/L, and the median was 666 IU/L. The upper limit of normality of CK established in our laboratory is 293 IU/L. Therefore, our patients presented a mean CK elevation of 4-fold the upper reference limit (range, 0.4-fold to

Table I

	Mean	SD	Min.	Max.
Age (years)	62.8	14.4	25	86
BMI	29.9	4.3	19.8	39.8
Operating time (min)	279.2	76.1	170	570
No. fused segments	1.9	1.5	1	9
CK (IU/L)	1185.8	1234.6	134	6028
CRP (mg/L)	28.2	22.3	2.1	142.2

BMI : body mass index ; CK : creatine kinase ; CRP : C-reactive protein ; SD : standard deviation.

20.5-fold). However, the median was 2.2-fold higher, and only 30% of patients presented CK values 4-fold higher than the upper normal limit.

Only 17 patients (17.7%, 95% CI 10.6%-26.8%) required rescue analgesia, consisting of a mean of 2.1 doses (range, 1-5). Mean duration of hospitalization was 8.5 days (median 7 days, range 2-64 days) and 87.5% of patients were discharged before 10 days.

Postoperative CK level negatively correlated with age ($r = -0.2$, $p = 0.03$), such that highest CK values were seen in the youngest patients (CK values : patients < 50 y 1794 IU/L ; patients 50-70 y 1161 IU/L ; patients > 70 y 940 IU/L ; ANOVA $p = 0.05$). Furthermore, CK levels were higher in men (1644 IU/L) than in women (844 IU/L) (t -test, $p = 0.002$).

A statistically significant correlation was found between CK values and the number of fused levels ($r = 0.45$, $p = 0.0001$), operating time ($r = 0.5$, $p = 0.0001$), and CRP concentration at 24 hours ($r = 0.4$, $p = 0.0001$). In contrast, there was no correlation with BMI ($r = 0.1$) or duration of hospitalization ($r = 0.1$).

CK level did not differ significantly between patients who did not require rescue pain therapy (1135 IU/L) and those who did (1421.5 IU/L). Nor was there a significant difference in the number of times CK level exceeded the normal upper limit (4.8 in the extra-pain group vs 3.8 in the regular-pain group). There was no significant relationship between CK level and the number of rescue analgesia doses administered.

Table II

	Extra pain	Regular pain	p
CK (IU/L)	1421	1135	Ns
x upper normal limit	4.8	3.8	Ns
Sex (female)	58%	57%	Ns
Diabetes	5.8%	12.6%	Ns
Depression	29.4%	31%	Ns
Hospitalization time (days)	8.9	8.4	Ns
CRP (mg/L)	20.4	29.7	Ns
Operating time (min)	290	276	Ns
No. fused segments	1.9	2	Ns

Ns : non-significant.

The group of patients with extra pain did not differ from those with regular pain for any of the variables analyzed (Table II).

DISCUSSION

Posterior spinal surgery led to an increase in CK values greater than twice the upper reference limit in more than half the patients in our cohort. Younger patients and males presented higher CK levels than their counterparts. Furthermore, statistically significant correlations were found between serum CK levels and variables related to surgical invasiveness, including the magnitude of the dissection (number of fused levels) and operating time. There was no association with the duration of hospitalization. Our results indicate that serum CK is a suitable marker of surgical aggression, regardless of patient age or sex. The availability of a valid parameter to estimate the aggressiveness of a surgical procedure facilitates analysis of the more invasive maneuvers with the aim of reducing iatrogenic injury, and the development of strategies to promote prompt recovery and limit sequelae. It is reasonable to expect that a parameter to estimate surgical invasiveness would show a relationship with two crucial variables in the surgical act : the number of fused levels and the operating time.

In our series, statistically significant differences in serum CK values were not found between the extra-pain and regular-pain patient groups, although

there was a trend to higher CK levels in those with extra pain (4.8-fold higher than upper limit vs. 3.8-fold in the regular-pain group). There were no differences between these groups with respect to sex, comorbidities, operating time, or number of fused levels.

CK has been considered a suitable indicator of muscle injury following various surgical procedures of the spine (1). In our research, the total CK level was determined, not the skeletal-muscle isozyme, CK/MM, taking into account the findings of Kumbhare *et al* (13). These authors demonstrated that in patients undergoing posterior spinal surgery, the MM fraction accounts for virtually the entire CK value both preoperatively and at the postoperative peak.

In some previous studies, postoperative CK levels have been associated with the size of the dissection, such that in more aggressive procedures, the values of this enzyme are elevated (5,1,13,27).

There is, however, controversy around this point because other authors have reported elevated CK values following procedures involving little surgical aggression (21). It has also been found that the pressure exerted by the retractors on the paraspinal musculature and the duration of this pressure (operating time) has an impact on serum CK values (9,12). A reduction in blood supply to the muscles caused by compression could explain this finding (11,24).

CK levels can be affected by several patient-related variables, such as the muscle mass, liver function, and age (7). The muscle mass depends on the amount of physical activity and is influenced by a person's sex (20) and weight (8); higher postoperative CK values have been found in men undergoing spine surgery than in women (10), as was seen in our series. With increasing age, there is a decrease in the paraspinal musculature as muscle fibers are replaced by fibrous tissue or fatty infiltration, which leads to a reduction in the effective muscle area (8). Our finding of a negative correlation between serum CK values and age supports this concept.

The relationship between invasiveness of surgery and the duration of postoperative pain is also a subject of debate. It has been suggested that persistent postoperative low back pain at middle term may be related to the trophic changes observed in the para-

spinal musculature following surgery, although the literature is not unanimous on this point. Gejo *et al* (5) reported that patients with greater involvement of the paraspinal muscles assessed by magnetic resonance imaging (MRI) presented a higher incidence of low back pain at six months following surgery. In the same line, Fan *et al* (4) found a significant relationship of pain with disability and degree of spinal muscle atrophy determined by MRI at one year. Datta *et al* (3) compared a group of patients in whom retractors were intermittently loosened during the procedure with another group in whom they were maintained, and found less severe muscle injury in the intermittent group. Nonetheless, the authors reported no significant differences regarding pain (VAS), disability (ODI), or quality of life (SF-36) at six months' follow-up between these patients and those with continuous retraction.

Weber *et al* (26) investigated histological changes in the paraspinal muscles following surgery and their relationship with persistent pain. No correlations were found between muscle changes and pain intensity either in patients treated with a first surgery or those undergoing revision surgery. The authors concluded that factors other than muscle injury should be considered to explain the persistent pain. Furthermore, atrophy of the paraspinal musculature has also been found in patients treated by anterior spinal surgery and in patients with low back pain who have not undergone any surgical procedure (16). Asymmetry of the paraspinal musculature greater than 10% has even been found in patients with no history of low back pain (19).

It seems clear that more invasive surgery, as established by operating time and the number of treated vertebral segments, causes greater muscle injury, which can be evaluated by serum CK levels. However, the published data are not conclusive as to whether the degree of muscle injury is related to the degree of pain postoperatively and at middle term. Despite this uncertainty, it has been proposed that by reducing the skin incision and/or extent of dissection using minimally invasive surgery (MIS) techniques, there will be less tissue injury, with a secondary decrease in postoperative pain, shorter duration of hospitalization (22,27), and faster return to normal daily activity (14).

Some authors have suggested that less invasive surgery is also related to a better clinical outcome at middle term (2,15,21,27). However, in a prospective study comparing patients operated by MIS and patients treated with a standard open approach, Wang *et al* (25) found no significant differences in low back pain or disability after twenty-six months of follow-up. It is beyond the objectives of the present study to analyze the effectiveness of MIS compared to open approaches, but it is well recognized that numerous variables unrelated to the procedure, such as psychological, social, and work-related factors, have a considerable influence on the long-term outcome of low-back pain surgery (17,18).

Pain intensity is usually estimated using a process measure, such as a visual or numerical rating scale. However, these instruments are not routinely used by the nursing staff in our hospital. As was mentioned in the methods section, we follow our hospital protocol for administration of intravenous analgesic treatment with metamizole and paracetamol, and rescue analgesia with subcutaneous meperidine. The decision to administer rescue analgesia is at the discretion of the attending nurses, based on their clinical judgment that a patient is experiencing excessive pain. It could be argued that it would be preferable to know the intensity of the pain, since the decision to administer rescue analgesia is affected by the individual bias of the nurse. However, the number of nurses caring for these patients is small, so the risk of bias would be similar in all cases. We are aware of the methodological limitation implied by the lack of an objective measure of pain intensity in the study. Nevertheless, we believe that our research offers an essentially pragmatic perspective: the use of rescue analgesics and the amount given is an objective process measure (6,12) that provides a satisfactory estimation of the intensity of postoperative pain.

We should recognize that the small number of patients in the extra-pain group is a limitation of the study. CK values were higher in this group than in patients with regular pain (1421.5 vs. 1135 IU/L) and the number of times that values exceeded the upper limit of normality was also higher in the extra-pain group (4.8 vs. 3.8). The lack of significant

differences could be attributed to the limited size of the sample.

In conclusion, the results of this study indicate that serum CK values in the immediate postoperative period enable estimation of the surgical aggression on the paraspinal musculature during posterior spinal surgery. We did not find a significant relationship between the levels of this enzyme and immediate postoperative pain, although there was a trend to this association that would need to be confirmed in prospective studies with adequate statistical power.

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