Changes in creatine phosphokinase (CK) concentrations after minor and major surgeries in children

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Background. During surgery, damage occurs to muscles in the area of the operation. The few studies that have examined creatine phosphokinase (CK) values after surgery have been in adults. The only study in children was after cardiac surgery. Understanding the normal enzyme pattern of change may help to differentiate malignant hyperthermia, anaesthesia-induced rhabdomyolysis and elevated CK values resulting from inherited muscle disease in cases in which these are suspected. The aim of this study was to delineate the normal rise of CK after minor and major surgery in children.

Methods. A total of 71 patients aged 1 month–17 yr were studied. From the cohort of 71 patients, 46 underwent elective surgery (14 major, 32 minor) and in 25 the surgery was designated as an emergency surgery (21 major, 4 minor). The anaesthesia protocol was similar for both groups with halothane induction and isoflurane maintenance. Owing to its possible effect on CK, succinylcholine was avoided during the study.

Results. The mean values of CK concentration before and after surgery were 63.1 iu litre−1 and 151.5 iu litre−1, respectively. The median CK elevation (range) for the major and minor surgery groups was 43 iu litre−1 (4–647) and 10 iu litre−1 (28 to 122), respectively (P<0.0001).

Conclusions. CK concentrations in the major surgery group were significantly higher than the minor surgery group. This profile can contribute to the evaluation of patients who present with the possibility of malignant hyperthermia, anaesthesia-induced rhabdomyolysis and underlying muscle disease. Any rise of CK concentration above what is expected should prompt further investigation.

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Creatine phosphokinase (CK) is a large i.m. protein made up of two distinct polypeptide subunits, M and B. Three iso-enzymes of CK are found in human tissue: CK-MM (skeletal muscle), CK-MB (cardiac muscle), and CK-BB (brain). In adult human skeletal muscle, 99% of CK activity is CK-MM. CK catalyses the reversible transfer of energy-rich phosphate from creatine phosphate to adenosine diphosphate, thus forming adenosine triphosphate (ATP). The ATP formed is utilized mainly in muscle myofibrils during muscle contraction. The molecular structure of these large proteins prevents them from being released from the host tissue into the bloodstream, except in muscle membrane injury. Serum concentrations of CK are increased after muscle is damaged by physical or biochemical injury. This has been reported after strenuous physical activity, trauma, crush injury, myositis, muscular dystrophy, i.m. injection, convulsions, myocardial infarction, malignant hyperthermia and drugs such as amino-phyline and succinylcholine. Other enzyme markers for skeletal muscle injury: aldolase, enolase, aspartate aminotransferase, and lactate dehydrogenase isoenzyme 5 are not as specific as CK. CK measurement in serum has remained the best overall marker for detection and monitoring of skeletal muscle diseases and damage.
The few studies that have examined CK values after surgery have been in adults. The only study in children was after cardiac surgery. The importance of knowing the 'normal' pattern of change after surgery is obvious. During surgery, damage occurs to muscles in the area of the operation. Therefore, knowing the normal enzyme pattern may help to differentiate malignant hyperthermia and elevated CK values attributable to inherited muscle disease in cases in which these entities are suspected.

The aim of this study was to describe the normal rise of CK after minor and major surgery in children.

Methods

The study was approved by the local and the Israeli MOH ethics committees.

Children (age <18 yr) admitted for elective and emergency surgery were eligible for the study. Inclusion criteria were: low risk patients (ASA-I, ASA-II). Patients with chronic diseases and patients with known muscle or heart disease in the patient or family members were excluded.

After informed consent provided by the guardians, according to the Israeli law, the patients were allocated to two groups based on the subjective impression of the degree of muscle involvement as a result of the surgical procedure:

I—major surgery, including intra-abdominal and intra-thoracic;

II—minor surgery, such as orchiopexy,inguinal hernia and hydrocele repair, anoplasty and drainage of pilonidal abscess.

Blood samples (1 ml) for CK concentrations were drawn before surgery (during the pre-induction of anaesthesia) and 6–24 h after the surgery.

All the elective patients (except for six teenagers who preferred i.v. induction), received general anaesthesia which was induced with halothane up to 4%, fentanyl 3 mcg kg\(^{-1}\) and atropine 0.01 mg kg\(^{-1}\). In the emergency cases, when i.v. line was already present, anaesthesia was induced by i.v. propofol 2–2.5 mg kg\(^{-1}\). Tracheal intubation in both groups was facilitated by rocuronium 0.5 mg kg\(^{-1}\). In both groups, anaesthesia was maintained with isoflurane 1–1.5% and fentanyl in incremental dose as necessary. All patients received standard monitoring during anaesthesia. Owing to its possible effect on CK, succinylcholine was avoided during the study. Fortunately, none of our patients had a clinical indication for its use.

**CK measuring method**

N-acetyl cysteine activated CK activity was monitored on a Hitachi 917 instrument (Boehringer Mannheim GmbH, Germany). In the routine assay, CK catalyses the reversible phosphorylation of creatine by ATP. The ATP produced is measured by coupling the hexokinase and glucose-6-phosphate dehydrogenase reactions to the CK reaction. Normal CK values (SI units) were 12–80 iu litre\(^{-1}\) in males and 10–55 iu litre\(^{-1}\) in females.

**Statistical methods**

The Wilcoxon signed rank test was used for the comparison of pre and post surgery CK concentrations. The \(t\)-test was performed to compare the means of two groups and Mann–Whitney test to compare the distributions between the two groups when appropriate.

Results

A total of 74 patients aged 1 month–17 yr were studied. Three patients with extremely high preoperative CK concentrations were excluded (data for these patients is shown in Table 1). From the cohort of 71 patients, 46 underwent elective surgery (14 major, 32 minor) and in 25 the surgery was designated as an emergency surgery (21 major, 4 minor) (Table 2).

### Table 1 Clinical features of children excluded from the study

<table>
<thead>
<tr>
<th>Patient</th>
<th>M/F</th>
<th>Age at operation</th>
<th>Operation</th>
<th>Preoperative CK (iu litre(^{-1}))</th>
<th>Postoperative CK (iu litre(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>13 yr</td>
<td>Gangrenous appendicitis</td>
<td>291</td>
<td>117</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>3 days</td>
<td>Repair of tracheo-oesophageal fistula with oesophageal atresia</td>
<td>778</td>
<td>1596</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>1 day</td>
<td>Hirschprung’s disease (whole colon)</td>
<td>288</td>
<td>333</td>
</tr>
</tbody>
</table>

### Table 2 Patient characteristic data and surgery type. \(^*\)Age comparison between groups, \(P<0.0005\). \(^*\)Age comparison between groups, \(P<0.011\)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Female</th>
<th>Male</th>
<th>Age (months) range [mean (sd)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>71 (100%)</td>
<td>30 (42%)</td>
<td>41 (58%)</td>
<td>1–204 [81 (67)]</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>46 (65%)</td>
<td>19 (27%)</td>
<td>27 (38%)</td>
<td>1–204* [60 (66)]</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>25 (35%)</td>
<td>11 (15%)</td>
<td>14 (20%)</td>
<td>5–192* [118 (54)]</td>
</tr>
<tr>
<td>Minor surgery</td>
<td>36 (51%)</td>
<td>12 (17%)</td>
<td>24 (34%)</td>
<td>5–192* [60 (62)]</td>
</tr>
<tr>
<td>Major surgery</td>
<td>35 (49%)</td>
<td>18 (25%)</td>
<td>17 (24%)</td>
<td>1–204* [101 (67)]</td>
</tr>
</tbody>
</table>
CK concentration before surgery ranged between 10 and 133 iu litre\(^{-1}\) with a mean value of 63.1 (26.2) iu litre\(^{-1}\) and a median of 57 iu litre\(^{-1}\). CK concentration after surgery ranged between 15 and 770 iu litre\(^{-1}\) with a mean value of 151.5 iu litre\(^{-1}\) and a median of 93 iu litre\(^{-1}\). Ninety-four per cent of the patients had CK elevation after surgery, with 61% of the minor surgery cases (Fig. 1A) compared with 86% in the major surgery group (Fig. 1B) had postoperative CK concentrations above the normal range for age (\(P<0.02\)). Table 3 presents the clinical features of the 10 children with the highest CK response.

The children undergoing emergency surgery had lower preoperative CK values [52.5 (24.3) iu litre\(^{-1}\)], median 51 iu litre\(^{-1}\), than elective surgery patients [69 (26) iu litre\(^{-1}\)], median 66.5 iu litre\(^{-1}\) (\(P<0.015\)). Multivariate analysis has showed that both type (major/minor) and urgency (elective/emergency) of surgery were related independently to an increase in CK concentration. This increase was not associated with the preoperative CK concentrations.

Postoperative CK concentrations in the major surgery group were higher than the minor surgery group (\(P<0.001\)). The mean and median (range) CK concentration for patients before and after surgery in the major surgery group were 60.6 (28.1) iu litre\(^{-1}\), 53 iu litre\(^{-1}\) (10–123) and 220.5 (209) iu litre\(^{-1}\), 129 iu litre\(^{-1}\) (58–770) respectively and were 65.6 (24.4) iu litre\(^{-1}\), 59.5 iu litre\(^{-1}\) (31–133) and 84.4 (39.7) iu litre\(^{-1}\), 73.5 iu litre\(^{-1}\) (15–196) in the minor surgery group. The mean and median CK elevation (range) for the major and minor surgery groups were 159.9 (202) iu litre\(^{-1}\), 43 iu litre\(^{-1}\) (4–647) and 18.9 (28.8) iu litre\(^{-1}\), 10 iu litre\(^{-1}\) (–28 to 122), respectively (\(P<0.0001\)).

**Discussion**

To our knowledge this is the first study investigating CK values after surgery in children. Our results show a significant rise in the CK concentrations, mainly after major surgery. These results are consistent with the results published by Laurence,\(^2\) who studied both CK and myoglobin concentrations before and after surgery in adults. He studied 30 patients allocated to minor or major muscle-cutting surgery, based on the subjective impression of the surgeon. As in our results, CK concentrations were significantly higher in the major surgery group, peaked between days 1 and 2 and were still elevated 6 days after the surgery. Karr and

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**Table 3 Clinical features of children with the greatest CK response**

<table>
<thead>
<tr>
<th>Patient</th>
<th>M/F</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Operation</th>
<th>Sampling time (h)</th>
<th>Preoperative CK (iu litre(^{-1}))</th>
<th>Postoperative CK (iu litre(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>0.6</td>
<td>6</td>
<td>Hirschprung’s disease</td>
<td>7</td>
<td>123</td>
<td>770</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>0.3</td>
<td>4.5</td>
<td>Exploratory laparotomy, excision of teratoma</td>
<td>10</td>
<td>82</td>
<td>647</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>8</td>
<td>20</td>
<td>Appendectomy</td>
<td>21</td>
<td>100</td>
<td>674</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>0.7</td>
<td>6</td>
<td>Closing ileostomy</td>
<td>12</td>
<td>38</td>
<td>412</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>0.4</td>
<td>5</td>
<td>Hirschprung’s disease (resection of transverse and descending colon)</td>
<td>17</td>
<td>30</td>
<td>303</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>12</td>
<td>25</td>
<td>Excision of abdominal mass</td>
<td>18</td>
<td>65</td>
<td>654</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>7</td>
<td>18</td>
<td>Appendectomy</td>
<td>12</td>
<td>10</td>
<td>463</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>4</td>
<td>13</td>
<td>Nissen fundoplication</td>
<td>16</td>
<td>76</td>
<td>533</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>16</td>
<td>52</td>
<td>Sympathectomy</td>
<td>8</td>
<td>48</td>
<td>414</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>17</td>
<td>70</td>
<td>Sympathectomy</td>
<td>8</td>
<td>72</td>
<td>231</td>
</tr>
</tbody>
</table>

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colleagues\textsuperscript{5} studied CK concentrations in elderly patients after surgery for hip fracture. The peak values were seen on day 1 after operation. A gradual decline was noted and at day 5 after operation, 50\% of values were within the normal reference range. A similar pattern was also noted by Kraft and colleagues\textsuperscript{5} who studied CK concentrations 26 h after operation. The only study in children\textsuperscript{7} aimed mainly to assess the usefulness of troponin-T for monitoring postoperative cardiac damage. CK concentrations up to 1134 iu litre\textsuperscript{-1} were found 28 h after cardiac or great vessel surgery. The mean CK MB fraction was 6\% of the total CK.

Although it is possible that higher CK values may have been encountered on the second day, we did not consider it ethical to obtain additional blood samples after discharge. It was also regarded as unnecessary when related to data obtained in previous studies.\textsuperscript{2,5,6} The same anaesthesia protocol was used for all patients in order to avoid the variable effect of anaesthesia on CK concentrations. It may be speculated that longer duration of anaesthesia time in major surgery may also contribute to higher CK concentrations.

Unlike adults, in whom high CK values raise the possibility of myocardial infarction, knowing the ‘normal’ increase of CK after surgery in children is important when the possible complication of malignant hyperthermia, anaesthesia-induced rhabdomyolysis or a complication resulting from muscle disease may be anticipated. These ill-defined conditions can be easily differentiated by CK concentrations >1000 iu litre\textsuperscript{-1}.\textsuperscript{12,15} No postoperative complications were noted, thus eliminating this as a contributory factor for an increase in CK concentrations.

Although there were statistically significant differences between the ages of patients undergoing elective vs emergency surgery and minor vs major surgery, there was no statistically significant difference in preoperative CK concentrations between younger (\textlesssim 60 months) [73 (45) iu litre\textsuperscript{-1}] and older (>60 months) [66 (45) iu litre\textsuperscript{-1}], \(P=0.347\).

A possible methodological problem in this study was that the postoperative CK samples were taken 6–24 h after the operation. Nevertheless, most of the samples (78\%) were taken between 6 and 12 h (60\% in the major surgery group and 94\% in the minor surgery group). When compared, the CK concentrations drawn between 13 and 24 h were relatively higher [201 (218) iu litre\textsuperscript{-1}] compared with concentrations drawn between 6 and 12 h after operation [140 (142) iu litre\textsuperscript{-1}], but this was not significant (\(P=0.535\)).

**Conclusion**

We have found that the rise in CK after surgery in children can typically be 150 iu litre\textsuperscript{-1} after a major surgery but negligible after a minor surgery. This profile can contribute to the evaluation of those patients who present with the possibility of malignant hyperthermia, anaesthesia-induced rhabdomyolysis and underlying muscle disease. Any rise of CK concentrations above what is expected should prompt further investigation.

**Acknowledgement**

We thank Dr Geoffrey Collins and Prof. Michael Jaffe for their help and comments.

**References**