RE-DEFINING THE NORMAL ADRENOCORTICAL RESPONSE TO SURGERY


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BACKGROUND

Previous studies on surgical stress cortisol responses have used older, less-specific assays, have not differentiated by severity, or only studied procedures of a defined type. AIM of this study: to examine the adrenocortical response to surgery of varied severity, utilising a widely used cortisol immunoassay.

METHOD

- Euthyroid patients undergoing elective surgery enrolled prospectively.
- Samples taken at 8 am on surgery, induction and 1 hr, 2 hr, 4 hr and 8 hr after.
- Subsequent samples taken daily (8 am) until post-op day 5 or hospital discharge.
- Total cortisol measured using an Abbott Architect immunoassay
- Cortisol binding globulin (CBG) measured using a radioimmunoassay.
- Surgical severity classified by POSSUM operative severity scores.

RESULTS

Ninety-three patients underwent elective surgery: Major/Major+ (n=37), Moderate (n=33), and Minor (n=23) (Table 1).

TABLE 1

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Laparoscopic</th>
<th>Median Hosp. Stay (days)</th>
<th>Median op length (min)</th>
<th>Heart rate (bpm)</th>
<th>BMI (kg/m²)</th>
<th>Male:Female</th>
<th>Age (yrs)</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
</tr>
<tr>
<td>Neck; CT, Cardiothoracic</td>
<td>1000</td>
<td>1500</td>
<td>1500</td>
<td>1500</td>
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</tbody>
</table>

- Total cortisol (nmol/L)

* = significant difference between Minor and Moderate group.
** = significant difference between Moderate and Major/Major+ group.
*** = significant difference between Minor and Major/Major+ group.
**** = significant difference between Moderate and Major/Major+ group.

**TABLE 1**

Demographics of patients

<table>
<thead>
<tr>
<th>All (n=93)</th>
<th>Major/Major+ (n=37)</th>
<th>Moderate (n=33)</th>
<th>Minor (n=23)</th>
<th>Statistical comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>65.1 [51.0–68.0]</td>
<td>62.8 [51.1–68.3]</td>
<td>61.2 [51.0–68.0]</td>
<td>60.6 [51.0–68.0]</td>
</tr>
<tr>
<td><strong>P&lt;0.001</strong> (Kruskal-Wallis)</td>
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<tr>
<td>Male/Female</td>
<td>48/45</td>
<td>23/15</td>
<td>19/16</td>
<td>19/15</td>
</tr>
<tr>
<td><strong>P&lt;0.001</strong> (Kruskal-Wallis)</td>
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</tr>
<tr>
<td>Total cortisol (nmol/L)</td>
<td>1500</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peak cortisol (nmol/L)</td>
<td>1500</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Change in CBG from 0800h baseline (%): Moderate vs Major/Major+ ‡‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in FCI from 0800h baseline (%): Moderate vs Major/Major+ ‡‡</td>
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</tbody>
</table>

**FIGURE 2**

Perioperative cortisol response for patients classified by surgical severity (Minor: filled circles, dotted lines; Moderate: filled squares, dashed lines; Major/Major+: filled triangles, solid lines). (A) Serum total cortisol values (medians with error bars representing interquartile range). (B) Values normalised to 8 am baseline cortisol on the day of operation (median with error bars representing interquartile range).

**TIME COURSE OF CORTISOL RESPONSE TO SURGERY**

Serum cortisol levels during Minor procedures fluctuated around baseline levels during the procedure. In patients undergoing surgeries classified as Moderate, cortisol levels typically returned to baseline by 8am by 8 hrs after induction. Patients undergoing Major/Major+ surgeries demonstrated total serum cortisol levels comparable to baseline on post-operative Days 1-5 (Figures 2A and 2B).

**TIME COURSE OF CORTISOL BINDING GLOBULIN RESPONSE TO SURGERY**

Cortisol binding globulin (CBG) was measured serially in a subgroup of 18 patients (6 Minor, 6 Moderate, 6 Major/Major+). Consistent with previous reports CBG dropped acutely during surgery (Figure 3A). The free cortisol index (FCI) was calculated as the ratio of total cortisol to CBG at each timepoint: there was a rise (Figure 3B), which was more marked in the Major/Major+ group compared to the Moderate and Minor groups at the 4 hr and 8 hr timepoints.

**FIGURE 3**

(A) Perioperative CBG response normalised (%) to baseline 8 am value, and separated into different surgical severities. Comparison, using Tukey’s multiple comparisons test, of Minor vs Major/Major+: P<0.001; P<0.001; P<0.001; P<0.001; P<0.001; P<0.001; P<0.001; P<0.001. (B) Perioperative free cortisol index (FCI) response normalised (%) to baseline 8 am value, separated into surgical severities. Comparison, using Tukey’s multiple comparisons test, of Minor vs Major/Major+: P<0.001; P<0.001; P<0.001; P<0.001; P<0.001; P<0.001; P<0.001; P<0.001. (C) Perioperative cortisol response normalised (%) to baseline 8 am value, separated into different surgical severities. Comparison, using Tukey’s multiple comparisons test, of Minor vs Major/Major+: P<0.001; P<0.001; P<0.001; P<0.001; P<0.001; P<0.001; P<0.001; P<0.001. (D) Perioperative cortisol response normalised (%) to baseline 8 am value, separated into different surgical severities. Comparison, using Tukey’s multiple comparisons test, of Minor vs Major/Major+: P<0.001; P<0.001; P<0.001; P<0.001; P<0.001; P<0.001; P<0.001; P<0.001.

**CONCLUSIONS**

- Cortisol responses to surgery are positively correlated with operative severity.
- Stress cortisol levels are lower in older studies, but comparable to more recent studies (1,2).
- CBG levels drop acutely during surgery, leading to elevated free cortisol exposure.
- Physiological levels of cortisol return to baseline by post-operative day 1 even in Major/Major+ surgery.
- These data support a graded approach to hydrocortisone replacement in hypoadrenal patients depending on operative severity (3).

**REFERENCES**