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## Adrenal Function in Newborns Undergoing Surgery

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### Abstract

**Objective**—To measure cortisol, ACTH-stimulated cortisol and ACTH values in NICU-admitted newborn infants within 48 hours prior to surgery and to describe the relationship of these values to measures of clinical illness before and after surgery.

**Study Design**—In this prospective observational study, we measured baseline and ACTH-stimulated cortisol concentrations within 48 hours prior to surgery in newborn infants <44 weeks postmenstrual age and examined the relationship of these values to measures of illness severity both before and after surgery, including the score for neonatal acute physiology (SNAP) and use of vasopressors. ACTH concentrations were measured in a subset of the infants.

**Results**—Twenty-five infants were enrolled and had median [25<sup>th</sup> -75<sup>th</sup> percentile] baseline and ACTH-stimulated cortisol values of 7.1 [3.5-11.1] and 40.4 mcg/dl [22.6-50.6]. Preterm infants had significantly lower ACTH-stimulated cortisol values (median 21.6 vs.44.7 mcg/dl). There was no correlation between any of these values and either the pre-surgical or post-surgical measures of illness severity, nor the increase in SNAP scores after surgery. Infants receiving vasopressors peri-operatively had lower median ACTH-stimulated cortisol values (22.6 vs. 44.7 mcg/dl).

**Conclusion**—Pre-surgical cortisol values do not predict clinical response to surgical stress as measured by severity of illness scores but lower values were associated with vasopressor therapy. Further investigation would be required to determine how cortisol values are related to outcome and whether peri-operative glucocorticoid supplementation would be beneficial in this population.

### Keywords

adrenal insufficiency; hypothalamic-pituitary-adrenal axis; hydrocortisone; surgery; newborn; infants; cortisol; vasopressors; critically ill; hypotension

### Introduction

Many newborn infants admitted to Newborn Intensive Care Units undergo surgery and some of them will have unexplained cardiorespiratory deterioration postoperatively<sup>1</sup>. In adult

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surgical populations, relative adrenal insufficiency, or an inadequate cortisol response to stress, has been linked to hemodynamic instability and poor outcomes after surgery.<sup>2</sup> Recently, a post ACTH-stimulated cortisol value of less than 25 mcg/dl has been suggested to define relative adrenal insufficiency in critically ill adults.<sup>3</sup> In term and late preterm newborn infants, low random cortisol values suggestive of relative adrenal insufficiency have been found in the face of acute stress or illness.<sup>4, 5, 6</sup> Preterm newborn infants have also been reported to have low cortisol values during critical illness, and these low concentrations have been associated with the need for vasopressor support and with adverse outcomes<sup>7, 8, 9, 10, 11</sup> A stimulated cortisol of <17mcg/dl has been associated with adverse outcomes in this preterm population of infants.<sup>12</sup> An inability to increase cortisol levels in response to stress or illness in newborn infants could account for cardiovascular instability seen in some newborn infants after surgery and could potentially increase the risk of post-surgical complications. However, the prevalence of relative adrenal insufficiency in these infants is unknown. Additionally, little to no information exists on the relationship of pre-surgical cortisol values to measures of severity of illness after surgery and the ability of pre-surgical cortisol values to predict cardiovascular decompensation after surgery.

## Methods

### Patient Population

This study was a single site, prospective, observational study of newborn infants admitted to the University of New Mexico (UNM) Newborn Intensive Care Unit (NICU) between 2002 and 2009. Eligible patients included infants <44 weeks estimated gestational age (GA) who were admitted to the UNM NICU and were scheduled within 48 hours for a surgical procedure to be performed by a pediatric surgeon. Infants were excluded if they had received hydrocortisone within 96 hours prior to surgery or had a lethal chromosomal disorder. The institutional review board of the UNM Health Sciences Center approved the study and informed parental consent was obtained.

### Study Procedures

Data collected included infant demographics, diagnoses, surgical procedures as defined by the attending surgeon, initiation of vasopressors and glucocorticoids for the treatment of hypotension and severity of illness scores. Severity of illness was measured with the Score for Neonatal Acute Physiology (SNAP-1).<sup>13</sup> The pre-surgery SNAP-1 (SNAP) score was calculated for the 24 hours prior to surgery and the post-surgery SNAP score was calculated for the 24 hours after surgery. The delta SNAP was defined as the difference between the post-surgery SNAP and the pre-surgery SNAP.

Adrenal function studies were performed within 48 hours prior to the surgical procedure. One infant was studied 96 hours prior to surgery. This patient's data fell within the range for the remainder of the sample and therefore was included in the analyses. Blood (1 ml) was drawn for cortisol and adrenocorticotropic hormone (ACTH) concentrations, after which a low dose (1 mcg/kg) of cosyntropin (1-24 ACTH) was administered intravenously (IV).<sup>12</sup> Only a subset of infants had ACTH concentrations performed as approval and funding for ACTH concentrations was obtained later in the study. A second blood specimen (0.5 ml)

was drawn 60 minutes later for a stimulated cortisol concentration. Increment cortisol was defined as the difference between the stimulated and baseline cortisol values. Cortisol concentrations were measured by radioimmunoassay (Coat-a-count kit, DPC, Los Angeles CA) in the core laboratory of the General Clinical Research Center (GCRC) at UNM. Blood for ACTH testing was placed in a cold EDTA tube, centrifuged cold and frozen at -70°C until analysis by chemiluminescence immunoassay (Immulite 2000 instrument, DPC, Los Angeles, CA) in the clinical laboratory of the University Hospital.

### Statistical Analysis

Patient characteristics, SNAP scores and cortisol values were compared between groups using student's t test. Data that was not normally distributed was log transformed prior to analysis. Correlations of cortisol values with SNAP scores were analyzed with the Spearman rank correlation coefficient. Fisher's Exact test was used to compare proportions. Data are presented as mean  $\pm$  standard deviation or as median [25%-75% percentile]. The level of significance was set at  $p < 0.05$ . Statistical analysis was performed using NCSS 2007 (Hintze, J. (2006), Kaysville, Utah).

### Results

There were 136 infants in the NICU identified by screening to have a surgical condition of which 18% were enrolled, 34% of parents refused consent and almost 48% were not approached primarily because research nurses or parents were unavailable or infants underwent surgery before completing consent process. Twenty-five babies were enrolled and divided into 2 groups: those with surgery performed during the first postnatal week (Group 1) and those with surgery after the first week (Group 2). Population characteristics are shown in Table 1. The 2 groups of infants were significantly different in gestational age and birth weight. There was no difference between groups in gender, pre-surgical or post-surgical SNAP scores. Surgical procedures performed are outlined in Table 2.

Median [25-75%ile] baseline and ACTH-stimulated cortisol values for the entire study group were 7.1 mcg/dl [3.7-11.3] and 38 mcg/dl [23.7-52.6]. Eight infants (32%) had ACTH-stimulated cortisol values  $< 25$ mcg/dl, of which 83% were preterm vs term infants. One infant had ACTH-stimulated cortisol less than 17mcg/dl (baseline and stimulated cortisol values were 2.2 and 13.3 mcg/dl). This patient was small for gestational age with a birth weight of 1647 grams at 36 weeks GA and underwent a laparoscopic Nissen fundoplication at 32 days of age. No infant had an increment cortisol  $< 9$ mcg/dl. Baseline cortisol values were not different between groups; however, the ACTH-stimulated and increment cortisol values were significantly lower in group 2, as shown in Table 3. ACTH concentrations were obtained in 11 infants, including only one in Group 2 (Table 3).

Median [25-75%ile] SNAP scores significantly increased after surgery compared to before surgery in the overall study population (9 [3-15] vs.3 [2-9],  $p=0.01$ ) and in each study group (Table 1). Pre-surgical SNAP scores did not correlate with either baseline ( $\rho=-0.3$ ,  $p=0.1$ ) or ACTH-stimulated cortisol values ( $\rho=-0.3$ ,  $p=0.2$ ). The delta SNAP did not correlate with baseline or ACTH-stimulated cortisol values (Figure 1). Within each group, there was again no correlation of delta SNAP with baseline (group 1,  $\rho=-0.03$ ,  $p=0.9$ ; group 2,

$\rho=0.1$ ,  $p=0.8$ ) or ACTH-stimulated cortisol values (group 1,  $\rho=-0.3$ ,  $p=0.3$ ; group 2  $\rho=-0.03$ ,  $p=1$ ).

The other measure of severity illness collected was vasopressor administration. Six infants received vasopressors peri-operatively; two of these were initiated after surgery. There were more infants who received vasopressors when ACTH-stimulated cortisol values were  $<25$  vs.  $25$  mcg/dl (63% vs. 6%,  $p=0.007$ ).

One infant died within 48 hours after PDA ligation. This patient had baseline and ACTH-stimulated cortisol values of 7.9 and 21.6mcg/dl, respectively. The infant received vasopressors prior to surgery and was given hydrocortisone (1mg/kg) for vasopressor-resistant hypotension after surgery. No other infant received hydrocortisone after surgery.

## Discussion

In this prospective study of 25 infants undergoing surgery in the neonatal period, we found that 32% of the infants had ACTH-stimulated cortisol values  $<25$ mcg/dl, a value suggestive of glucocorticoid insufficiency in other ill populations.<sup>3</sup> These infants were more likely to receive vasopressors peri-operatively (63% vs 6%) and to be born prematurely (83% vs 16%). No infant had an increment cortisol value of  $<9$  mcg/dl, which has been associated with impaired vasopressor responsiveness and high mortality rate in other populations.<sup>14, 15</sup> The median ACTH level was 18.6 pg/ml, a value which would be considered low in the face of severe illness.<sup>16</sup> ACTH values above 28pg/ml suggest primary adrenal insufficiency.<sup>17</sup> In our study, the number of infants initiated on pharmacologic support for cardiorespiratory decompensation after surgery was small; therefore, it is difficult to draw any conclusions about the ability of pre-operative cortisol values to predict such decompensation. However, we found no correlation of pre-operative cortisol values, either baseline or stimulated, with postoperative severity of illness, strongly suggesting that pre-operative cortisol values do not predict post-operative course. This may have been due to the small sample size of this study.

This is the first study, to our knowledge, in which the primary objective was to investigate the incidence of relative adrenal insufficiency in newborn infants about to undergo surgery. We chose to undertake this investigation because a substantial percentage of neonates have been reported to experience unexplained hemodynamic decompensation after surgery. In one study of preterm and term infants (6-81 days old) who underwent PDA ligation, 28-35% experienced hemodynamic decompensation after surgery.<sup>1</sup> Among such infants, mortality rates have been reported to be as high as 33%.<sup>1, 18</sup> Although mortality can be attributed to a cause in a small percentage of some surgical cases,<sup>19</sup> most of this mortality remains unexplained. One possible contributing factor may be relative adrenal insufficiency, which has been described as a contributing factor in the adult population.<sup>2</sup>

Relative adrenal insufficiency has been suggested in other groups of neonates in whom lower cortisol values are associated with the need for vasopressors, and in whom hydrocortisone therapy leads to resolution of the cardiovascular insufficiency.<sup>5, 7, 10, 20</sup> Infants with inappropriately low cortisol response to stress would be at risk for hemodynamic compromise after surgery. This relationship was not apparent in our study;

however only 2 (8%) infants experienced such deterioration (initiation of vasopressors *after* surgery), clearly limiting our ability to evaluate this relationship.

Other investigators studying newborn hormonal responses to cardiac surgical stress found no significant difference in pre-operative mean cortisol values between survivors and non-survivors (9.5 mcg/dl, n=11 vs. 13.5 mcg/dl, n=4).<sup>21</sup> The same investigators tested a score for surgical stress in preterm and term newborn infants. They found that cortisol values correlated less well to the surgical stress score than did other metabolic responses and suggested that this was due to a poor cortisol response to stress in newborns.<sup>22</sup> Other studies of endocrine and metabolic response to surgery in newborns did not perform ACTH-stimulation tests and there were no postsurgical outcomes reported.<sup>23</sup>

The small size of this study is a limitation in evaluating the relationships between cortisol values to severity of illness. In particular, a larger study including more infants with cardiorespiratory decompensation after surgery and measurement of postoperative cortisol values would clarify these relationships. Another limitation in this study is the inclusion of broad variety of surgical problems. Because of the variation in surgical procedures, the post-surgical SNAP scores were not used in the analysis of correlations to cortisol values. Instead, each infant's change in SNAP from pre-surgery to post-surgery was used for analysis.

In summary, this prospective observational study found that a significant percentage of preterm infants who underwent surgery had ACTH-stimulated cortisol values below the threshold suggested for relative adrenal insufficiency in other populations. However, pre-operative cortisol studies did not predict the increase in severity of illness scores postoperatively in neonatal patients. Because this study population did not include a sufficient number of infants who experienced new cardiovascular insufficiency after surgery, the ability of pre-operative cortisol studies to predict that specific outcome remains unclear. Further study which includes measurement of postoperative cortisol values would lead to a more thorough understanding of how cortisol values might relate to outcome in the neonatal surgical population and help elucidate the role of glucocorticoid therapy.

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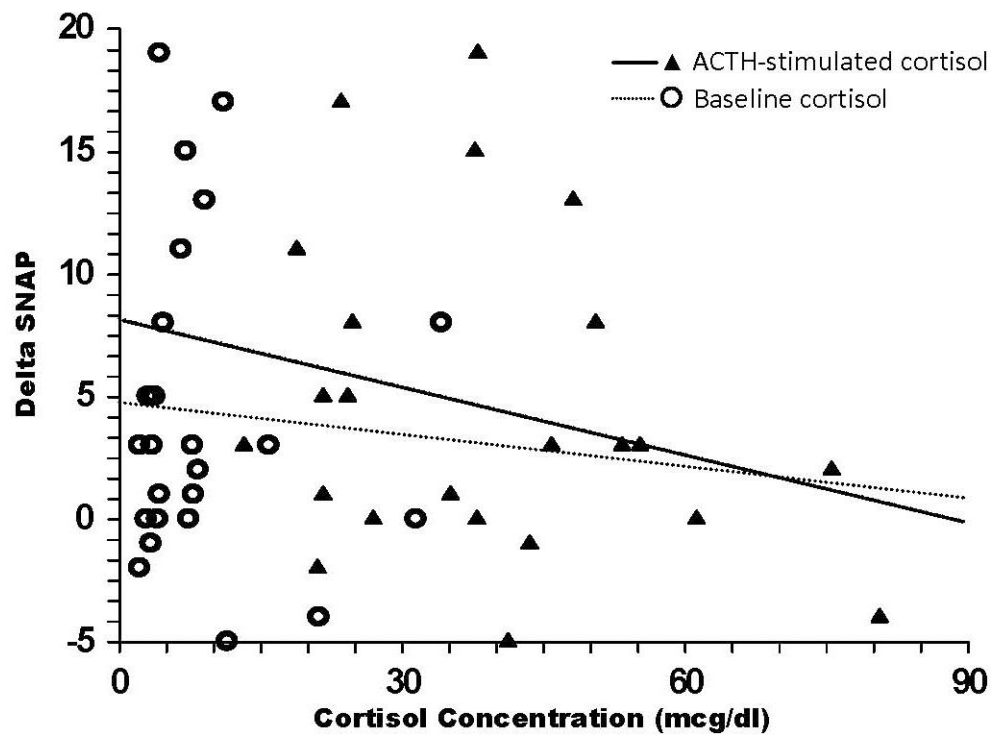
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**Figure 1.** Delta SNAP scores vs. pre-surgery cortisol values. There was no significant correlation between delta SNAP and baseline cortisol concentrations (dashed line, open circle) ( $\rho=-0.2$ ,  $P=0.4$ ) and no significant correlation between delta SNAP and ACTH-stimulated cortisol concentrations (solid line, solid triangle) ( $\rho=-0.3$ ,  $P=0.2$ ). One ACTH-stimulated cortisol value not shown (103 mcg/dl) but was included in analysis.  $\rho$ , rho; Delta SNAP, Post-surgery SNAP score minus pre-surgery SNAP score.



**Table 1**

## Demographics profile and SNAP scores

	Group 1 Surgery 7 days old n=19	Group 2 Surgery >7 days old n=6
Gestation (weeks)	37.7 ± 2.2 <sup>a</sup>	27.5 ± 4.5
Birth weight (grams)	2868 ± 551 <sup>a</sup>	930 ± 363
Male (%)	14 (74)	3 (50)
Postnatal age at surgery	3 [1-6] <sup>a</sup>	37 [22-51]
Pre-surgery SNAP	3 [1-11] <sup>b</sup>	3 [2-10] <sup>b</sup>
Post-surgery SNAP	7 [2-14]	10 [5-20]

Abbreviations: SNAP, Score for Neonatal Acute Physiology

Data are expressed as mean ± s.d. or as median [25%-75%ile]

Data are expressed as number of infants (%)

<sup>a</sup> Comparison between Group 1 vs. Group 2, P < 0.05

<sup>b</sup> Comparison between pre-surgery vs. post-surgery within each group, P < 0.05



**Table 2**

## Surgical procedure

<b>Group 1 Surgery 7 days old</b>	<b>Number of patients</b>
Repair of congenital diaphragmatic hernia	5
Second stage closure of gastroschisis	3
Primary closure of gastroschisis	2
Transanal Soave pull-through	2
Exploratory laparotomy, resection of jejunal atresia & appendectomy	2
Exploratory laparotomy & enterotomy with meconium extraction	1
Exploratory laparotomy & right hemicolectomy for colonic atresia	1
Exploratory laparotomy & duodenoduodenostomy	1
Placement of silo for gastroschisis	1
Small bowel resection & placement of silo for gastroschisis	1
<i>Group 2 Surgery &gt;7 days old</i>	<i>Number of patients</i>
Ligation of patent ductus arteriosus	3
Laparoscopic nissen fundoplication	1
Right frontal reservoir placement for hydrocephalus	1
Exploratory laparotomy & small bowel resection	1

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**Table 3**

Pre-surgery ACTH, baseline and ACTH-stimulated cortisol concentrations

	<b>Group 1 Surgery 7 days old</b>	<b>Group 2 Surgery &gt;7 days old</b>	<b>P-value<sup>a</sup></b>
Baseline cortisol (mcg/dl)	7.1 [3.5-15.9] n=19	6 [3.4-8.7] n=6	0.6
ACTH-stimulated cortisol (mcg/dl)	44.7 [33.1-56.7] n=18	22.6 [19.5-28] n=6	0.01
Increment cortisol (mcg/dl)	32.3 [22.4-42.5] n=18	15.8 [12.1-22.6] n=6	0.01
ACTH (pg/ml)	18.6 [11.9-28.8] n=10	56.5 n=1	

Abbreviations: ACTH, Adrenocorticotropic hormone  
Data are expressed as median [25%-75%ile]

<sup>a</sup>Comparison between Group 1 and Group 2

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