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ORIGINAL ARTICLE - PITUITARIES

Selective perioperative steroid supplementation protocol in patients undergoing endoscopic transsphenoidal surgery for pituitary adenomas

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Abstract

Background There is no consensus regarding the use of perioperative steroids for transsphenoidal pituitary surgery. We audited the effectiveness and safety of our selective perioperative steroid supplementation protocol in patients with pituitary adenomas.

Methods Two hundred ninety-seven patients underwent 306 endoscopic transsphenoidal surgeries for removal of their pituitary tumors. Steroids were given to those with an impaired hypothalamic-pituitary-adrenal (HPA) axis, age ≥ 60 years, clinical apoplexy, hyponatremia, or if the pituitary gland was not preserved at surgery. We excluded 111 patients in whom the integrity of the HPA axis could not be determined. We compared the incidence of early postoperative adrenal insufficiency and complications in 135 patients with intact HPA axes who underwent surgery without steroids (group A) with 60 patients who had compromised preoperative HPA axes and received perioperative steroids (group B). In addition, we audited the total number of protocol violations during this period.

Results Five patients (3.7%) in group A developed postoperative hypocortisolemia. There was no significant difference in the incidence of cerebrospinal fluid leak, diabetes insipidus, or hyponatremia between both groups. There were protocol deviations in 47 (15.4%) patients. Twenty one of these patients did not receive perioperative steroids in violation of the protocol, of whom 4 (19%) developed postoperative hypocortisolemia.

Conclusions Our steroid sparing protocol was both safe and effective. The 15% incidence of protocol deviations is a reminder that the rigorous usage of checklists is mandatory for successful clinical practice.

Keywords Pituitary adenoma · Perioperative · Steroid · Protocol deviation

Abbreviations

ACTH	Adrenocorticotropic hormone
AUC	Area under the curve
CSF	Cerebrospinal fluid
DI	Diabetes insipidus
FSH	Follicle-stimulating hormone
GH	Growth hormone
HPA	Hypothalamic-pituitary-adrenal
ICU	Intensive care unit
IGF-1	Insulin-like growth factor-1
LH	Luteinizing hormone
ROC	Receiver operating characteristic
T4	Thyroxine
TSH	Thyroid-stimulating hormone

This article is part of the Topical Collection on *Pituitaries*

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Introduction

The endoscopic transsphenoidal approach is presently the preferred method of pituitary adenoma resection [23]. Tumor removal carries the risk of postoperative secondary adrenal insufficiency with consequent hypotension, hyponatremia, and other symptoms of hypocortisolemia [25]. Controversy exists regarding whether to universally administer perioperative steroids for these patients or to use perioperative steroids only in selected patients. Of late, there has been a trend toward adopting the latter as multiple studies have demonstrated its safety and efficacy [2–4, 7, 9–11, 17, 21, 24, 27, 29], including a recent randomized controlled trial [24]. While randomized controlled trials are closely supervised and monitored for appropriate implementation of protocols, non-adherence to protocols in general clinical practice is bound to occur more frequently; however, this data is not available for pituitary surgery. Thus, despite the growing body of evidence supporting its effectiveness and safety, pituitary surgeons have not uniformly adopted the practice of withholding steroid replacements in patients who have an intact hypothalamic-pituitary-adrenal (HPA) axis preoperatively, instead preferring to institute a uniform policy of steroid use for all patients regardless of the integrity of the HPA axis [5]. In this retrospective study, we evaluated our existing selective perioperative steroid supplementation strategy for patients undergoing endoscopic transsphenoidal resection of pituitary adenomas. We studied the occurrence of early postoperative adrenal insufficiency and audited the compliance to the protocol to determine whether perioperative steroids were supplemented or withheld inappropriately.

Methods

We retrospectively collected data from our electronic medical records on 297 adult patients who underwent 306 endoscopic transsphenoidal surgeries for pituitary adenomas between 2013 and 2018. Patients with Cushing's disease were excluded. All patients had preoperative measurement of 8 AM cortisol, thyroid-stimulating hormone (TSH), total and free thyroxine (T4), prolactin, growth hormone (GH), and insulin-like growth factor (IGF)-1. Additionally, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured in women, and the 8 AM testosterone level was measured in men.

Assessment of HPA axis

Patients with 8 AM cortisol levels ≥ 16 μg/dL were considered to have a normal HPA axis, while < 3.6 μg/dL indicated hypocortisolism. Patients with 8 AM cortisol levels between 3.6 and 15.9 μg/dL, were assessed with the adrenocorticotropic hormone (ACTH) stimulation test. The ACTH stimulation test was performed with 25 units of intramuscular Acton Prolongatum® (porcine sequence corticotropin, Ferring, Saint-Prex, Switzerland; which is equivalent to 250 mcg of Synacthen®). The serum cortisol was measured after 60 min using the chemiluminescence immunoassay. A post-ACTH serum cortisol level ≥ 18 μg/dL indicated an intact HPA axis, while any value less than this was taken as an inadequate response.

Perioperative steroid protocol

Our protocol was based on the study by Inder and Hunt [10]. Patients ≥ 60 years of age, those who presented with apoplexy or with comorbidities including hyponatremia, coronary heart disease, or bronchial asthma, received perioperative steroids regardless of their preoperative serum cortisol levels. If the patient was on steroids from elsewhere, we continued steroids regardless of age. This protocol was approved by our Institutional Review Board (IRB No 7558, dated 09/08/2011).

Perioperative steroid cover consisted of intravenous hydrocortisone 25 mg 6th hourly on the day of surgery (day 0), followed by oral prednisolone 10 mg in the morning and 5 mg in the evening on day 1, and prednisolone 5 mg in the morning and 2.5 mg in the evening on day 2. These patients were asked to continue prednisolone 5 mg once daily until their 3-month follow-up visit, when prednisolone was withdrawn and the 8 AM cortisol level was tested to assess recovery of the HPA axis.

Those with 8 AM cortisol levels ≥ 16 μg/dL were asked to discontinue steroids, while those with cortisol levels < 3.6 μg/dL were continued on steroids long term. Patients with cortisol levels between 3.6 and 16 μg/dL underwent an ACTH stimulation test. Those with post-ACTH stimulation cortisol levels ≥ 18 μg/dL were advised to stop steroids, and those with < 18 μg/dL were advised to continue prednisolone and educated on hydrocortisone cover during stressful situations.

Radiology

The tumor volume and maximum diameter were measured on preoperative magnetic resonance imaging (MRI), and the tumors were classified according to the Hardy-Wilson grading (A-E) [28]. The presence of apoplexy and invasion into the cavernous sinus/sphenoid sinus was also noted.

Surgery

All patients were operated through the endoscopic transsphenoidal route. We performed an intracapsular tumor excision in order to identify and preserve the pituitary gland that was usually seen as a thin, yellow orange sheet on the inner aspect of the tumor capsule [6]. The surgeon noted the presence of altered blood and cystic degeneration, extent of invasion, and preservation of the adenohypophysis. If the surgeon was completely unable to preserve the normal pituitary gland, steroids were administered and continued postoperatively. If there was an intraoperative CSF leak, a lumbar subarachnoid drain was kept in situ for 5 days. Tissue was submitted for histopathological examination and immunohistochemistry for GH, prolactin, ACTH, TSH, FSH, LH, and alpha subunit. Tumors immunonegative for all hormones were not classified further as transcription factor expression was not assessed.

Assessment of extent of resection

Extent of resection was confirmed with a hyperacute MRI scan done 8–12 h after surgery and at follow-up after 3 months. It was categorized into gross total resection (no visible residue), subtotal resection (≤ 10% residue), and partial resection (> 10% residue).

Group A and group B

For the purpose of this retrospective study, patients with an intact HPA axis were categorized into group A (135), while those with a definite impairment of the HPA axis were assigned to group B (60). The remaining 111 patient procedures were excluded because HPA axis integrity could not be ascertained prior to surgery, because of protocol deviations or because the surgeon was unable to preserve the adenohypophysis at surgery prompting an intraoperative injection of hydrocortisone followed by postoperative steroids (5 patients) (Table 1).

Postoperative management

All patients were managed in the intensive care unit (ICU) for 12–24 h and then transferred to the ward. Serum 8 AM cortisol levels were checked on postoperative days 1, 2, 3, and 7 in those patients who did not receive steroids. Patients with 8 AM cortisol levels < 3.6 μg/dL were initiated on steroid replacement. Those who experienced severe symptoms of hypocortisolemia such as persistent vomiting or lethargy and those who developed persistent hyponatremia were also started on intravenous hydrocortisone after collecting blood for random cortisol. If the random serum cortisol returned as normal, they were not considered to have developed hypocortisolism.

We recorded the incidence of postoperative hypocortisolism in group A. We also noted the incidence of postoperative hyponatremia and diabetes insipidus (DI) in all patients. The majority of our patients were from out-of-state and were asked to stay close to the hospital and come back for review 1 and 2 weeks after surgery.

Table 1 Details of patients excluded from the analysis

Reason for exclusion	Number of patients (111)
Steroids started elsewhere (HPA axis integrity unknown)	23
Protocol deviation	
Intact HPA axis yet given steroids	21
Age > 60 but steroids not given	9
ACTH stimulation test not done	17
Steroids withheld wrongly	12
Steroids administered	5
Preoperative hyponatremia	15
Clinical apoplexy (started steroids but HPA axis not tested)	12
Age ≥ 60 years, steroids given, but HPA axis not tested	9
Gland not seen/not preserved at surgery	5

ACTH, adrenocorticotrophic hormone; *HPA*, hypothalamic-pituitary-adrenal

Statistical analysis

Data was entered into a Microsoft Access database and analyzed using SPSS version 23.0 (Armonk, NY: IBM Corp). Descriptive statistics were used for patient characteristics and surgical details. Chi-square was used for categorical variables, and Student *t* test or non-parametric test (Mann-Whitney) was used for continuous variables when required. We assessed the accuracy of 8 AM cortisol to predict the need for ACTH stimulation testing using the area under the curve (AUC) on the corresponding receiver operating characteristic (ROC) curve. We used the ROC curve to derive threshold cortisol values and calculate the resultant sensitivity and specificity.

Results

Demographic data of the two groups (Table 2)

Patients in group B were predominantly male ($p = 0.002$) and significantly older ($p = 0.005$). They also had larger tumors and more frequently presented with apoplexy, hypothyroidism, and secondary hypogonadism (in females) compared with the patients in group A ($p < 0.05$).

Surgery and postoperative details (Table 3)

Group A patients had more extensive tumor removal ($p = 0.041$) compared with those in group B. They also had a slightly longer duration of hospital stay (mean 6.6 vs. 5.6 days, $p = 0.021$) There was no significant difference between the two groups in terms of incidence of postoperative hyponatremia and DI. As expected, patients in group B developed more permanent cortisol deficiency than those in group A ($p < 0.001$). No patient in our series developed meningitis.

Table 2 Preoperative clinicoradiological characteristics of groups A and B

Features	Group A (135) *N* (%)	Group B (60) *N* (%)	*p* value
Age (years)	39.1 ± 9.9	44.5 ± 13.1	*0.005*
Gender			
Male (116)	71 (52.6)	45 (75)	*0.002*
Female (79)	64 (37.5)	15 (25)	
Tumor type			
Non-functional	25 (18.5)	20 (33.3)	*0.014*
Somatotroph	61 (45.2)	9 (15)	
Lactotroph	2 (1.5)	0 (0)	
Mixed somatomamotroph	19 (14.1)	4 (6.7)	
Gonadotroph	20 (14.8)	23 (38.3)	
Silent corticotroph	8 (5.9)	4 (6.7)	
Tumor size (mm)*	24.4 ± 10.6	32.7 ± 11.4	*< 0.001*
Tumor volume (ml)*	6.5 ± 9.8	12.7 ± 12.1	*0.001*
Microadenomas	13 (9.6)	0 (0)	*0.013*
Wilson-Hardy Grade:			
A (30)	18 (13.3)	4 (6.7)	*0.015*
B (94)	46 (34.1)	17 (28.3)	
C (126)	44 (32.6)	32 (53.3)	
D (21)	6 (4.4)	5 (8.3)	
E (13)	8 (5.9)	2 (3.3)	
Invasive			
Yes	61 (45.2)	29 (48.3)	0.684
No	74 (54.8)	31 (51.7)	
History of apoplexy			
Yes	0 (0)	8 (13.3)	*< 0.001*
No	135 (100)	52 (86.7)	
Radiological apoplexy			
Yes	8 (5.9)	6 (10)	0.309
No	127 (94.1)	54 (90)	
Preoperative hypothyroidism			
Yes	29 (21.5)	50 (83.3)	*< 0.001*
No	106 (78.5)	10 (16.7)	
Preoperative secondary hypogonadism in males			
Yes	54 (76.1)	32 (71.1)	0.252
No	10 (14.1)	4 (8.9)	
Not adequately assessed	7 (9.9)	9 (20)	
Preoperative secondary hypogonadism in females			
Yes	24 (37.5)	11 (73.3)	*0.012*
No	40 (62.5)	4 (26.7)	

*Data missing for 1 patient

The last column is devoted to *p* values. Those in italics are significant. The non-significant *p* values are upright

Table 3 Surgery and postoperative details

Outcome	Group A (135) *N* (%)	Group B (60) *N* (%)	*p* value
Extent of excision			
Total	75 (55.6)	28 (46.7)	*0.041*
Subtotal	55 (40.7)	24 (40)	
Partial	5 (3.7)	8 (13.3)	
CSF leak			
Yes	27 (20)	13 (21.7)	0.79
No	108 (80)	47 (78.3)	
Postoperative hyponatremia			
Yes	59 (43.7)	30 (50)	0.415
No	76 (56.3)	30 (50)	
Postoperative diabetes insipidus			
Yes	6 (4.4)	4 (6.7)	0.516
No	129 (95.6)	56 (93.3)	
Length of postoperative hospital stay (days)	6.6 ± 3.2	5.6 ± 2.7	*0.021*
Postoperative radiation			
Yes	39 (28.9)	17 (28.3)	0.94
No	96 (71.1)	43 (71.7)	
Cortisol deficiency at follow-up*			
Yes	4 (3.1)	34 (82.9)	*< 0.001*
No	126 (96.9)	7 (17.1)	

*24 lost to follow-up

The last column has *p* values. Those in italics are significant. The insignificant ones are upright

Postoperative cortisol levels and steroid administration in group A

Following the 135 operations, 28 (20.7%) patients received steroids in the postoperative period for the following reasons:

i) Five (3.7%) had biochemically proven hypocortisolism, 4 of whom were asymptomatic. The low cortisol levels occur around the third postoperative day (mean 3.25 ± 1.8 days) (Table 4), and the mean day 1 cortisol level was 16.1 ± 16.1 μg/dL (range 0.8–39.7), which was lower than the mean day 1 cortisol level of the patients that did not develop hypocortisolism (24.0 ± 13.8 μg/dL, $p = 0.21$).

ii) Eleven (8.1%) were started on fludrocortisone because of persistent hyponatremia after ruling out other causes.

iii) Nine (6.6%) complained of fatigue, nausea, and vomiting after 48 h (mean 2.5 ± 1.7 days) that

Table 4 Details of the 5 patients in group A that developed postoperative hypocortisolemia

Age/gender	Hospital stay (days)	Wilson-Hardy grade	8 am cortisol (μg/dL)	Post-ACTH cortisol (μg/dL)	Extent of resection	Type of adenoma	Postoperative day of low cortisol
21/M	13	D	12.14	26.53	Subtotal	Gonadotroph	9
51/M	4	B	17.1	NA	Total	Non-functional	1
31/F	12	Micro	12.7	30.93	Subtotal	Somatotroph	1
35/M	10	C	8.63	29.3	Subtotal	Non-functional	6
40/M	6	C	6.97	21.15	Total	Non-functional	3

ACTH, adrenocorticotrophic hormone; *NA*, not applicable

prompted the immediate administration of intravenous hydrocortisone; however, none had hypocortisolism or hyponatremia when the biochemical results returned and steroids were not continued.

iv) Three (2.2%) patients were started on steroids for other reasons, namely, stress cover for infection ($n = 2$) and visual deterioration due to a postoperative hematoma ($n = 1$).

The mean postoperative 8 AM cortisol levels in 130 patients who did not develop hypocortisolism were 24.0 ± 13.8 μg/dL, 17.4 ± 8.4 μg/dL, and 15.9 ± 6.7 μg/dL on days 1, 2, and 3 respectively. This translated to an 80% increase in the mean cortisol level on postoperative day 1 compared with the mean preoperative level of 13.3 ± 4.7 μg/dL ($p < 0.001$).

Permanent cortisol deficiency

Recovery of the HPA axis could not be determined in 5 patients who had no follow-up, but in the remaining 130 patients in group A, only 4 (3.1%) developed permanent hypocortisolism. Among the patients who did not require steroids in the postoperative period, none developed cortisol deficiency on follow up.

Serum cortisol cut-off for employing the ACTH stimulation test

We evaluated the accuracy of various 8 AM cortisol cut-off values between 3.6 and 15.9 μg/dL in predicting the presence of an intact HPA axis on the ACTH stimulation test using an ROC curve. However, no threshold value of cortisol had sufficient sensitivity or specificity (AUC = 0.588).

Protocol deviations

Among the 306 endoscopic transsphenoidal procedures, there are a total of 47 (15.4%) protocol violations (Table 1). This included 21 patients who had a preserved HPA axis and 5 patients who did not have ACTH stimulation test done but were unintentionally started on perioperative steroids. In the remaining 21 patients, steroids were inadvertently withheld: 9 who were above 60 years of age and 12 in whom the ACTH stimulation test was not done despite being indicated. Of these 21 patients, 4 (19%) developed hypocortisolism and had to be administered postoperative steroids. Five more were given steroids for other reasons (3 for persistent hyponatremia and 2 for lethargy and vomiting).

Discussion

Rationale for selective perioperative steroid cover

Patients with pituitary adenomas, who have an intact HPA axis, demonstrate a surge in serum cortisol levels during surgery to almost 80 to 500% of baseline [5, 20]. Postoperatively, cortisol levels have been shown to peak at around 6 h after surgery [5, 30], leading to the introduction of steroid-sparing protocols in which only patients with preoperative adrenal insufficiency receive perioperative steroid cover [11, 14, 21, 24, 27]. In our study too, the patients in group A who did not develop postoperative hypocortisolism showed an 80% increase in their mean cortisol level on postoperative day 1. Other arguments in favor of a steroid-sparing protocol include the fact that perioperative steroid administration renders postoperative assessment of the HPA axis difficult, often resulting in patients being unnecessarily discharged on long-term steroids [1, 21]. Steroids also inhibit vasopressin release in patients with suboptimal reserve, resulting in a higher incidence of postoperative DI [20]. Prolonged administration of steroids causes weight gain, development of Cushingoid features, elevated blood glucose, elevated blood pressure, recurrent infections, proximal myopathy and deep vein thrombosis.

Postoperative hypocortisolism

We found that only 5 (3.7%) of the 135 group A patients who were operated without steroid cover developed biochemically proven hypocortisolism, 4 of whom were asymptomatic. This parallels the reported 1–13% incidence of early postoperative adrenal insufficiency in patients with an intact HPA axis prior to surgery [25]. Fortunately, as in our study, patients who do develop postoperative hypocortisolism are either asymptomatic or experience only minor symptoms such as nausea and vomiting, rather than major adverse events like hypotension or death [19, 21, 24]. Interestingly we found that the 9 (6.6%) additional patients, who were initially started on hydrocortisone for persistent vomiting and lethargy, were later found to have normal serum cortisol levels. This shows that the early symptoms of fatigue, nausea, and vomiting are non-specific, and their occurrence after pituitary surgery is probably multifactorial.

A recent single-center randomized controlled trial on 36 patients showed that withholding perioperative steroids for patients with an intact HPA axis was not associated with increased hypocortisolism, hyponatremia, or other complications when compared with those who were administered perioperative steroids [24]. Even in our series, there was no significant difference in the rates of postoperative hyponatremia or adrenal insufficiency between groups A and B. There was however a small, albeit significant, difference in the mean duration of postoperative hospital stay between both groups (group A (6.6 days) vs. group B (5.6 days), $p = 0.021$) probably due to the extra day required for the ACTH stimulating test.

Of the 5 patients in group A that developed early postoperative hypocortisolemia, 4 had persistent adrenal insufficiency 3 months following surgery, while in one patient, steroid supplementation could be discontinued indicating a temporary damage to the adenohypophysis. Five patients with intact HPA axes were excluded from group A in the analysis because they were administered steroids intraoperatively when the surgeon was unsure of the preservation of the pituitary gland. Interestingly the HPA axis of two of these patients recovered on long-term follow-up, confirming that a small remnant of viable adenohypophyseal tissue is compatible with eventual recovery of the HPA axis. In fact, current data maintains that an improvement in pituitary function in at least 1 hormone axis may be noted in over 20% of patients undergoing endoscopic pituitary surgery, with the HPA axis being the most likely to recover [13].

Adherence to protocol

Although we had an established protocol in place, we found that protocol deviations occurred in 47 (15.4%) patients. While administering steroids in patients with an intact HPA are unlikely to have serious consequences, it was the withholding of steroids in 21 (6.9%) patients (9 elderly patients and an additional 12 in whom the HPA axis was not adequately tested) that is of concern. The incidence of hypocortisolism when the protocol was violated was 19%, which was significantly higher than the 3.7% seen in group A. This clearly indicates that our protocol had a sound basis; the violation of which, although not resulting in serious untoward events, nevertheless had the potential to do so. It is well recognized that implementation of guidelines, protocols, and checklists effectively reduces adverse outcomes in surgery, and a protocol deviation rate of more than 10% for clinical trials is considered excessive [8, 12, 18]. However, while protocols used in well-conducted randomized controlled trials are highly supervised and monitored, non-adherence to protocols in general clinical practice is bound to occur more frequently. In a study evaluating an emergency medical services system, a protocol deviation rate of about 16% resulted in a 5% incidence of complications [22].

In our setting, we attributed the protocol deviations to the frequent rotation of neurosurgical residents through the unit and inadequate communication between the surgeons and anesthesiologists. After analyzing the findings of our audit, we incorporated additional sections in our checklists to ensure that inadvertent administration or withholding of perioperative steroids was minimized, as recommended by Laws et al. [12]. Nonetheless, merely following a protocol does not guarantee a reduction in adverse outcomes as multiple other factors are involved in ensuring safe patient care such as clinical acumen and expertise of the treating team, vigilant monitoring, and an overall commitment to delivering quality patient care. In our series, hypocortisolemia was promptly detected in the early postoperative period and managed appropriately.

Postoperative cortisol surge and its use as a predictor of long-term HPA axis integrity

The magnitude of the intraoperative cortisol surge seems to depend on which part of the day the patient is being operated on with a more modest rise seen in patients operated in the afternoon compared with those operated in the mornings [5]. This is probably due to the diurnal variation in ACTH/cortisol levels. Zada et al. [30] found that 65% of their patients had first postoperative day 8 AM cortisol levels of > 25 μg/dL. In our series, there was an 80% increase in mean serum cortisol levels on the first postoperative day, and 42% of the patients had a level > 25 μg/dL. The mean cortisol level on day 1 for the 5 patients who developed postoperative hypocortisolism was 16.1 μg/dL, which was almost 8 μg/dL lower than for those who did not develop hypocortisolism, although it did not attain statistical significance.

Based on a single day 0 or day 1 postoperative cortisol level, it might be possible to predict HPA axis integrity [14–16, 26]; however, Zada et al. [30] preferred noting the degree of surge and found that a > 25 μg/dL increase in cortisol level on day 1 compared with the preoperative level best predicted preservation of the HPA axis. More recently a recovery room cortisol > 27 μg/dL was found to be an accurate predictor of preserved HPA axis function [19].

Limitations

The main limitations of this study were its retrospective nature and the significant number of protocol deviations; however, our goal was to audit the effectiveness of an already established protocol since it mirrors actual practice as opposed to a carefully monitored prospective study. The 5 patients lost to follow-up in group A may have diminished the quality of our data. From this study, we were unable to calculate a higher preoperative 8 AM cortisol threshold for doing the ACTH stimulation test. Future studies with a larger sample size might be able to arrive at less strict cut-offs, thereby reducing the number of patients who would require the ACTH stimulation test.

Conclusions

Withholding perioperative steroids in patients with an intact HPA axis is safe in endoscopic pituitary surgeries. Patients who develop postoperative vomiting, fatigue, or hyponatremia often do not have hypocortisolism. Clinicians need to be alert to the rather common occurrence of protocol deviations in routine clinical practice and should institute steps to improve the implementation of checklists.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval and informed consent The perioperative steroid protocol approved by the Ethics Committee of our Institutional Review Board (IRB No 7558, dated 09/08/2011). For this retrospective study no formal consent was required.

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