Chapter 9
Steroid Management in Patients Undergoing Surgery for IBD

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Introduction

Often faced with the challenge of operating on steroid-treated patients with inflammatory bowel disease (IBD), colorectal surgeons must be well versed in the perioperative steroid management of this patient cohort. Historically, standard practice has entailed stress-dose or high-dose perioperative steroids in these patients undergoing surgery to prevent perioperative adrenal insufficiency (AI), cardiovascular collapse and death. Stress-dose steroids typically consist of hydrocortisone 100 mg intravenous (IV) given preoperatively and continued every 8 h postoperatively with a taper down to the preoperative dose over 2–3 days [1]. However, this practice is anecdotal and largely based on case reports from the 1950 s [2, 3] demonstrating cardiovascular collapse and death in 2 patients whose steroids were abruptly discontinued before surgery.

Furthermore, perioperative high-dose steroids are not without consequence and have been associated with impaired wound healing, hyperglycemia, hypertension, fluid and electrolyte imbalance, immunosuppression and psychological effects [4]. It has been suggested that the typical recommendation for supplementation with 200–300 mg of hydrocortisone per day is supraphysiologic and a much smaller (maximum of 150 mg/day) dose is necessary to overcome surgical stress [5]. While suppression of the hypothalamic-pituitary-adrenal (HPA) axis is known to occur with chronic corticosteroid supplementation [4], the amount and duration of steroid exposure necessary to suppress an appropriate response to surgical stress is unknown, nor is the

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Table 9.1 PICO questions

P (patients)	I (intervention)	C (comparator)	O (outcomes)
Steroid-treated patients with or without IBD undergoing colorectal or non-colorectal surgery	Low-dose perioperative steroids	High-dose or stress-dose perioperative steroids	Perioperative hemodynamic instability, adrenal insufficiency, morbidity, mortality, infectious complications
Patients with or without IBD, previously treated with steroids within 1 year undergoing colorectal or non-colorectal surgery	No corticosteroids	High-dose or stress-dose perioperative steroids	Perioperative hemodynamic instability, adrenal insufficiency, morbidity, mortality, infectious complications

duration of time necessary to overcome this HPA axis dysfunction [6]; some reports suggest this may take up to a year [7]. Thus, stress-dose steroids have even been advocated for patients previously treated with corticosteroids within the past year.

Over the past 6 decades, several studies in IBD and non-IBD patients have challenged the treatment algorithms for the use of perioperative stress-dose steroids. Yet, there remains great variability in perioperative steroid dosing for IBD patients undergoing colorectal surgery [8]. In this chapter, the literature pertaining to perioperative steroid dosing is reviewed and followed by our recommendations for steroid management in patients with IBD undergoing colorectal surgery.

Search Strategy

Relevant PICO (Population, Intervention, Comparator, Outcome) questions were generated (Table 9.1). A Medline and PubMed search was conducted for publications in the English language between January 1952 and November 2015 using the following search terms: (‘inflammatory bowel disease’ or ‘IBD’ or ‘ulcerative colitis’ or ‘Crohn’s’ or ‘organ transplant’ or ‘transplant’ or ‘rheumatoid arthritis’ or ‘steroid-treated’) and (‘corticosteroid’ or ‘steroid’) and (‘colorectal’ or ‘colorectal surgery’ or ‘surgery’ or ‘surgical’ or ‘operation’ or ‘operative’ or ‘perioperative’) and (‘stress-dose’ or ‘high-dose’ or ‘low-dose’ or ‘dosing’ or ‘coverage’ or ‘previous steroid’) and (‘adrenal insufficiency’ or ‘hemodynamic’ or ‘outcome’ or ‘complication’ or ‘morbidity’ or ‘mortality’). We also searched the reference section of each relevant article to identify additional articles pertaining to this topic. Retrospective and prospective, observational and randomized studies were included. Given the paucity of studies investigating IBD patients undergoing colorectal surgery, the search was expanded to include organ transplant recipients and other non-IBD steroid treated patients undergoing non-colorectal surgery.

Results

Over the years, several studies have been performed to assess the clinical utility and optimal dose of perioperative corticosteroids in steroid-treated patients undergoing surgery (Table 9.2). Initial studies challenging the concept of stress-dose steroids were performed in an era where there were serious concerns about operative wound healing. In these studies, patients underwent surgery without any perioperative steroids, and clinical parameters and HPA function were evaluated. In 1962, Solem and Lund reported 30 patients whose steroids had been stopped more than 4 weeks before surgery undergoing various surgical procedures (IBD undergoing major colorectal surgery, n = 4) without perioperative steroid cover and showed no impending hemodynamic collapse with this management [9]. Two studies investigated patients on steroids at the time of surgery who were operated on without perioperative steroids, measured HPA axis testing and clinical parameters. Hypotension attributed to AI occurred in 4 out of 125 patients combined [10, 11].

In a follow up study, Kehlet and Binder showed that preoperative ACTH stimulation testing correlated with perioperative HPA function in 48 steroid treated patients undergoing surgery (colorectal, n = 7) without perioperative steroids, but no patients had perioperative hemodynamic instability or required stress-dose steroids [12]. In 1981, Knudsen performed a retrospective study evaluating 250 steroid-treated IBD patients undergoing major colorectal surgery [13]. In 50 patients, perioperative steroid cover was provided whereas the remaining 200 patients underwent surgery without perioperative steroids. The study included 3 groups of patients: (1) patients on steroids at the time of surgery (n = 48); (2) patients whose steroids were stopped 1 week to 2 months before surgery (n = 76); and (3) patients off steroids greater than 2 months before surgery (n = 126). Intraoperative hypotension occurred in 29 patients (11.6 %) but was less common in the cohort off steroids more than 2 months before surgery (5.6 %). In 9 patients, intraoperative rescue hydrocortisone was given, although none of these patients had proven biochemical evidence of adrenocortical insufficiency. Of 8 patients developing postoperative hypotension, 2 patients on steroids at the time of surgery who underwent surgery without steroid cover were thought to have AI (1 biochemically proven). These early studies suggested the need for perioperative steroids in patients on steroids at the time of surgery. However the optimal perioperative steroid dose necessary to prevent AI and the utility of stress-dose steroids remained unclear at that time.

Subsequent studies evaluated various perioperative steroid dosing regimens consisting of low-dose steroids or maintaining patients on their preoperative steroid dose without a stress-dose. In 1981, the utility of a single preoperative stress-dose (hydrocortisone 100 mg) versus no stress-dose followed by reinstitution of the patient's preoperative steroid dose after surgery was prospectively studied in 61 steroid-treated patients with rheumatoid arthritis undergoing 107 major or minor orthopedic operations [14]. The authors found no significant difference in the need for perioperative rescue steroids in patients treated with stress-dose steroids (24 %) or not (17 %). In a small study of 14 steroid-treated patients (IBD, n = 7) compared

Table 9.2 Studies evaluating perioperative steroid dosing

First author (year)	Patients studied	Intervention	Study design	N	Outcome	Quality of evidence
Solem (1962) [9]	Patients previously treated with steroids/various surgeries (n = 4 IBD/CRS).	No periop steroids	R	30	No unexplained death attributed to AI	Very low
Jasani (1968) [10]	RA/anterior synovectomy	No periop steroids	PO	21 steroid treated vs. 20 controls	1 patient with abnormal preop ACTH had hypotension responsive to steroids.	Very low
Kehlet (1973) [11]	Steroid-treated patients undergoing various major/minor operations	No periop steroids	PO	104	3 patients with hypotension and low cortisol thought to be AI	Low
Knudsen (1981) [13]	IBD/CRS	200 with no periop steroids, 50 received steroids	R	250	11 cases of hypotension treated with steroids/ possible AI	Very low
Lloyd (1981) [14]	RA/Orthopedic surgery	Stress-dose vs. usual daily dose.	PO	61	No difference in periop steroid supplementation between the 2 groups	Very low
Symreng (1981) [15]	Various patients (n = 7 IBD, n = 16, CRS)	If impaired ACTH stim test > HC 25 mg IV preop then 100 mg IV/24 h. If normal ACTH stim test: no periop steroids. Return to usual daily dose postop.	PO	14 steroid-treated patients and 8 steroid-naïve controls	No hemodynamic instability	Very low

First author (year)	Patients studied	Intervention	Study design	N	Outcome	Quality of evidence
Bromberg (1991) [16]	Renal transplant patients admitted w/significant physiologic stress	Usual daily dose	PO	40	No unexplained hemodynamic instability	Very low
Bromberg (1995) [17]	Renal transplant patients/various surgeries	Usual daily dose	PO	52	No clinical or laboratory evidence of adrenocortical insufficiency	Very low
Friedman (1995) [18]	Renal-transplant or RA/major orthopedic surgery	Usual daily dose	PO	28	All patients with endogenous adrenal function. No unexplained hemodynamic instability.	Very low
Glowniak (1997) [20]	Various (colorectal n=2) with positive ACTH stim test	Stress-dose vs. placebo. Return to usual daily dose postop.	RCT	18	No episodes of AI. One in each group with hypotension.	Very low
Thomason (1999) [21]	Organ transplant/gingival surgery	Stress-dose vs. placebo. Return to usual daily dose postop.	RCT	20	No hemodynamic instability	Very low
Mathis (2004) [19]	Organ transplant/lymphocele drainage	Stress-dose vs. no steroid. Return to usual daily dose postop.	R	58	No hypotension, arthralgia, ileus, mental status changes. Blood glucose higher with stress-dose	Very low
Zaghiyan (2011) [24]	IBD/CRS previously on steroids within 1 year	No periop steroids	R	49	No difference in hemodynamic instability	Low
Zaghiyan (2012) [22]	IBD/CRS	HDS vs. LDS	RO	32	No unexplained hemodynamic instability	Very low

(continued)

Table 9.2 (continued)

First author (year)	Patients studied	Intervention	Study design	N	Outcome	Quality of evidence
Zaghiyan (2012) [23]	IBD/CRS	HDS vs. LDS	R	97	No difference in hemodynamic instability	Moderate
Aytac (2013) [25]	IBD/CRS	Stress-dose vs. usual daily dose	R	235	More tachycardia with stress-dose otherwise no difference in hemodynamic instability	Moderate
Zaghiyan (2014) [26]	IBD/CRS	HDS vs. LDS	RCT	92	Non-inferiority of LDS vs. HDS with respect to postural hypotension; no difference in hemodynamic instability. More infections with HDS.	High

IBD inflammatory bowel disease, *CRS* colorectal surgery, *RA* rheumatoid arthritis, *ACTH* adrenocorticotropic hormone, *HDS* high-dose steroids, *LDS* low-dose steroids, *R* retrospective, *PO* prospective observational, *RO* retrospective observational, *RCT* randomized controlled trial

We recommend that steroid-treated patients undergoing major colorectal surgery be managed with low-dose perioperative steroids in the perioperative period (*evidence quality high; strong recommendation*)

with 8 steroid-naïve controls undergoing various operations (major colorectal surgery, n = 16), Symreng and colleagues showed that steroid-treated patients with abnormal preoperative ACTH-stimulation testing (n = 6) can be managed with low-dose steroids (hydrocortisone 25 mg IV at the induction of anesthesia followed by 100 mg IV over the next 24 h) followed by reinstitution of the preoperative dose, whereas patients with a normal ACTH stimulation testing can be managed without steroids on the day of the operation [15]. This steroid regimen resulted in perioperative plasma cortisol levels similar to steroid-naïve patients and no patients had signs of hemodynamic collapse.

In the 1990s, Bromberg and colleagues performed 2 prospective cohort studies evaluating renal transplant recipients admitted with significant physiologic stress (n = 40) or for various operations (n = 52) who were managed with only their usual steroid dose [16, 17]. Whereas almost all patients had normal urinary cortisol levels and no signs of unexplained clinical hemodynamic insufficiency, ACTH-stimulation testing appeared to overestimate adrenal dysfunction in a majority of patients. In 1995, Friedman and colleagues prospectively evaluated 28 renal-transplant or rheumatoid arthritis patients on an average prednisone dose of 10 mg/day undergoing major orthopedic surgery [18]. All patients had endogenous adrenal function and no episodes of AI occurred. In 2004, another retrospective study of 58 pancreas and kidney transplant recipients undergoing lymphocele drainage showed no difference in hypotension, arthralgia, mental status changes, ileus or wound healing in patients treated with stress-dose steroids or not, but patients treated with stress-dose steroids had more hyperglycemia [19].

Two underpowered randomized-controlled studies were performed in the 1990s. The first was a randomized, double-blind study of 18 steroid-treated patients with positive ACTH stimulation test undergoing various surgical procedures (2 colorectal) managed with either stress-dose steroids or placebo plus the patient's baseline steroid dose [20]. Two episodes of hypotension occurred, one in each group, both related to bleeding or hypovolemia. The authors concluded that patients with secondary AI do not experience hypotension or tachycardia when given only their preoperative steroid dose for surgical procedures. The second study was a randomized, double-blind, crossover study of 20 organ transplant recipients on prednisone (5 – 10 mg) undergoing gingival surgery, randomized to hydrocortisone 100 mg IV or placebo preoperatively during their first surgery and the opposite for the second surgery [21]. Despite several cases of abnormal ACTH stimulation testing, no patients developed perioperative hypotension or tachycardia.

With these studies, the concept of maintaining steroid-treated patients on their preoperative steroid dose in the perioperative period emerged. Despite this, colorectal surgeons managing IBD patients on high doses of preoperative steroids undergoing major colorectal surgery remained reluctant to apply this practice [1, 8]. Recently, our group performed several studies comparing low-dose steroids (LDS) versus high-dose steroids (HDS) in steroid-treated IBD patients undergoing major colorectal surgery. Our LDS protocol entailed one-third IV hydrocortisone equivalent to the daily preoperative steroid dose (IVED) given at the time of surgical incision, then one-third IVED every 8 h postoperatively, followed by a taper. For

patients off steroids at the time of surgery, no perioperative steroids were given. HDS entailed hydrocortisone 100 mg IV given preoperatively, then every 8 h after surgery followed by a taper to oral prednisone over 3 days. On hospital discharge, steroids were either discontinued or tapered.

In 2012, we performed a pilot study evaluating 32 steroid-treated IBD patients (10 patients on steroids up until surgery and 22 patients treated with steroids in the past year) managed with LDS [22]. Hypotension occurred in 16 % of patients, but all cases resolved with no intervention, fluid bolus, or blood transfusion and no patients were treated with vasopressors or high-dose corticosteroids for AI. We then compared LDS (n = 54) versus HDS (n = 43) in IBD patients on steroids (n = 48) or previously treated with steroids (n = 49) undergoing major colorectal surgery [23, 24]. For patients previously treated with steroids, median duration since last steroid dose was 4 months (range: 0.1 – 12 months) and median maximum steroid dose in the past year was equivalent to prednisone 25 mg/day (range: 5 – 60 mg/day). Aside from a higher incidence of tachycardia in patients previously treated with steroids managed with HDS [24], we found no significant difference in hemodynamic instability between the 2 patient groups and no patients required rescue high-dose steroids for AI.

Another study performed by Aytac and colleagues in 2013, retrospectively analyzed 48 IBD patients on steroids and 187 patients off steroids at the time of proctocolectomy [25]. Eighty-nine patients were treated with stress-dose steroids and 146 without. There was more sinus tachycardia in patients managed with stress-dose steroids. While there were no episodes of adrenal crisis, one patient in the stress-dose group was readmitted with hypotension, fatigue and bloating and diagnosed with AI. In 2014, our group performed a prospective, randomized non-inferiority study evaluating 92 steroid-treated IBD patients undergoing major colorectal surgery randomized to HDS or LDS [26]. LDS were found to be non-inferior to HDS with respect to our primary outcome, absence of postural hypotension on postoperative day 1, which occurred in 95 % of patients randomized to HDS versus 96 % of patients assigned to LDS, p = 0.007. This study included 41 patients previously treated with steroids (median duration since last steroid dose of 4 months; interquartile range: 2 – 6 months), of which 25 were randomized to LDS (no perioperative steroids given). There was no difference in hemodynamic instability between the 2 patient groups and no patients were treated with rescue HDS for AI. There was, however, an insignificant trend toward more infectious complications in HDS (16 %) versus LDS-treated patients (4 %); p = 0.11.

Recommendations Based on Data

Based on various retrospective and observational studies and few randomized prospective studies, stress-dose steroids appear to be unnecessary in IBD patients undergoing major colorectal surgery. Several studies in both IBD and non-IBD patients have suggested that patients can be maintained on their usual preoperative

steroid dose in the perioperative period. For patients previously treated with steroids within the past year, perioperative steroids can be avoided altogether [9, 13, 24, 26]. While preoperative ACTH stimulation and perioperative plasma cortisol levels may be evaluated, these tests tends to overestimate adrenal insufficiency and a majority of patients do not experience hemodynamic instability even when perioperative steroids are held altogether [11, 12, 15–17, 20]. Thus a low-dose perioperative steroid protocol consisting of the intravenous equivalent to the patient's preoperative dose appears to not only be sufficient, but may avoid infectious complications associated with high-dose steroids. Based on the available data, we recommend that steroid-treated IBD patients undergoing major colorectal surgery be managed with low-dose perioperative steroids in the perioperative period (*evidence quality high; strong recommendation*).

Personal View of Data

In our view, high-dose perioperative steroids are unnecessary and may increase perioperative risk. In our practice we maintain patients on their preoperative steroid dose in the perioperative period. Our perioperative protocol entails one-third IVED given at the time of surgical incision, then one-third IVED every 8 h postoperatively, followed by a taper. For patients off steroids at the time of surgery, no perioperative steroids are given. Patients are monitored closely in the perioperative period and any unexplained hemodynamic instability is followed by ACTH stimulation test. If patients are unresponsive to conservative measures and ACTH stimulation testing is positive, then high-dose steroids are given. In our experience, however, no patients have required additional high-dose steroids for AI with this protocol.

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