Review Article

Perioperative "stress dose" of corticosteroid: Pharmacological and clinical perspective

Geetanjali T. Chilkoti, Anshul Singh, Medha Mohta, Ashok Kumar Saxena

Department of Anesthesiology and Critical Care, University College of Medical Sciences and Guru Teg Bahadur Hospital, Shahdara, New Delhi, India

Abstract

Various exogenous steroid preparations have been in use for a wide range of indications. We, as an anesthesiologist often encounters a surgical patient receiving chronic steroid therapy. Perioperative use of steroid is associated with major complications such as full-blown adrenal crisis in the perioperative period due to the secondary adrenal insufficiency. Henceforth, comes the role of the perioperative "stress-dose" of steroids to mitigate this rare but potentially fatal complication. There have been opposing views regarding the need and the appropriate dosage of the perioperative steroids. The present review discusses the changing concept of perioperative "stress dose" of corticosteroids, its pharmacokinetics, clinical relevance, and the related controversies such as the need and the appropriate dose.

Keywords: Perioperative steroids, perioperative implications, "stress dose" of exogenous steroids

Introduction

Steroids, since their introduction in 1935, have been used for a wide range of indications. Initially, its indication was restricted to Addison's disease, but their anti-inflammatory and immuno-modulating property form the basis of their numerous indications and widespread use. Fraser *et al.* (1952), for the first time, reported the adrenal insufficiency which presented as intractable intraoperative hypotension during a major orthopedic surgery in a patient on chronic steroid therapy.[1] The sudden preoperative withdrawal or inadequate preoperative dose of corticosteroid was hypothesized to be the culprit and therefore, the concept of perioperative supraphysiologic "stress dose" corticosteroid (up to four times of baseline) arose to avoid the precipitation of adrenal crisis.[2,3] Various controversies have been linked to this concept over the last few decades. Therefore, the objective of the present review is to evaluate the changing concept of perioperative "stress dose" of corticosteroids, its pharmacokinetics, clinical relevance, and the related controversies such as the need and the appropriate dose.

A thorough and comprehensive literature search in PubMed medical databases was performed with the keywords "perioperative steroids" and "stress doses of steroid." The data search retrieved 44 items, out of which 21 articles were relevant which comprised case reports, research articles, meta-analysis, and review articles. The relevant articles have been incorporated in the present review.

Physiologic Effects and Indications of Steroids

The glucocorticoids exert a wide variety of physiological effects and pharmacological actions. The glucocorticoid affects the metabolism of carbohydrates, proteins, fats, water,

Address for correspondence: Dr. Geetanjali T. Chilkoti, A-1404, Jaipuria Sunrise Greens, Ahimsa Khand, Indirapuram, Ghaziabad - 201 014, Uttar Pradesh, India.
E-mail: geetanjalidr@yahoo.co.in

Access this article online

Quick Response Code:

Website: www.joacp.org

DOI: 10.4103/joacp.JOACP_242_17

How to cite this article: Chilkoti GT, Singh A, Mohta M, Saxena AK. Perioperative "stress dose" of corticosteroid: Pharmacological and clinical perspective. J Anaesthesiol Clin Pharmacol 2019;35:147-52.

and electrolytes. Cortisol stimulates gluconeogenesis by liver resulting in increased blood glucose concentrations, reduction of protein stores essential in all body cells caused by both decreased protein synthesis, and increased catabolism of proteins already in cells. Cortisol promotes mobilization of fatty acids from adipose tissue and enhances oxidation of fatty acids in cells. Cortisol is essential for excreting a water load and hydrocortisone has a relatively weak salt retaining and potassium wasting effect except for large doses, i.e., 300 mg in a day. Hydrocortisone, 25 mg is comparable to 0.1 mg of fludrocortisone in terms of mineralocorticoid activity. It affects the calcium metabolism by antagonizing the action of vitamin D on gut, and thus reducing its absorption.

Cortisol is needed for the muscle functioning and central nervous system. Therefore, muscle weakness, apathy, depression, and psychosis are manifestations of Addison's disease. Cortisol has antiinflammatory effects, reflecting its ability to stabilize lysozyme membranes, decrease the release of inflammation causing lysozymes, and decrease capillary permeability that prevents loss of plasma protein into tissues. In cardiovascular system, it increases blood pressure by a variety of mechanisms involving actions on the kidney and vasculature. In the vascular smooth muscle, they increase sensitivity to pressor agents such as catecholamines and angiotensin II, while reducing nitric oxide-mediated endothelial dilatation. In the gut, it inhibits the secretion of prostacyclin and increases gastric acid secretion, thus increasing the predisposition for peptic ulcer. Cortisols are necessary for the production of pulmonary surfactant and maturation of various enzyme systems in the liver in fetus. In the endocrine system, it has direct action on thyroid stimulating hormone and thus suppresses thyroid axis. Glucocorticoids in supraphysiological doses cause hypothalamic–pituitary–adrenal (HPA) suppression or adrenocortical atrophy and is described ahead in detail.

The various indications for supplemental corticosteroids include deficiency states such as acute or chronic adrenal insufficiency, allergies, asthma, aspiration pneumonitis, cerebral edema, lumbar disc diseases, autoimmune disorders, such as arthritis, collagen diseases, ocular inflammation, ulcerative colitis, and myasthenia gravis. In anesthesia, it has been commonly used for its antiemetic effect, for providing postoperative analgesia and also for treatment of postintubation laryngeal edema.[4] Adrenal suppression or insufficiency (AI) is the failure of the adrenal cortex to secrete sufficient amounts of corticosteroids and remains a first-line indication for exogenous steroid therapy. Adrenal suppression may be broadly divided into two categories: primary and secondary. Primary AI is characterized by destruction of the adrenal cortex (Addison's disease), and the causes include idiopathic infections, autoimmune, hemorrhage, and sepsis. Secondary AI is characterized by atrophy of the adrenal cortex, secondary to the disease process that affects the anterior pituitary [adrenocorticotropic hormone (ACTH) secretion] or hypothalamus [corticotropin-releasing (CRH) secretion], or due to exogenous chronic corticosteroid therapy.

Pharmacokinetics and Choice of Corticosteroid Preparation

Systemically administered steroids are metabolized in the liver by hepatic P-450 system and then excreted renally. In the liver, hydrocortisone is metabolized by conjugation to tetrahydrocortisone and prednisolone by hydroxylation and conjugation. The oral bioavailability of hydrocortisone is 50% and of methylprednisolone and dexamethasone, it varies from 50 to 80%. When administered orally, the plasma half-life of most is 1–3 h (e.g., cortisol: 90 min, prednisolone: 2–3.5 h, and prednisone: 3.4–4 h), but it does not reflect the biological half-life. Biological half-life correlates with the antiinflammatory activity as it reflects the duration of influence on target tissues and ranges from 8 (hydrocortisone) to 72 h (betamethasone). The biological half-lives last beyond their elimination half-lives that range from 1 to 5 h. In clinical scenario, hepatic and renal disease prolongs and enzyme induction shortens the duration of action. Prodrugs such as cortisone and prednisone are converted in the liver to their active metabolites, hydrocortisone, and prednisolone. The pharmacokinetic profile of methylprednisolone is similar to prednisolone. In the blood, it is present in both bound and free form, the latter being biologically active. It is bound to cortisol-binding globulin (CBG) which has high affinity but low capacity; once it is saturated, cortisol is bound to albumin. Hydrocortisone and prednisolone is highly protein bound when compared to dexamethasone. Presence of estrogen affects CBG concentration and it includes pregnancy, use of oral contraceptives, etc.[5] Liver disease and nephrotic syndrome reduces the concentration of albumin leading to prolongation of their half-lives. Therefore, the steroid doses should be lowered in all aforementioned clinical conditions. However, topically administered (lungs, skin, joints) steroids too allow systemic absorption.

All the steroid molecules have varying degree of glucocorticoid and mineralocorticoid activity. The glucocorticoid property is responsible for regulating metabolism and inflammation, whereas mineralocorticoid regulates sodium and water balance. Synthetic corticosteroids administered for glucocorticoid effects include prednisolone, prednisone, methylprednisolone, betamethasone, dexamethasone, and triamcinolone. Fludrocortisone is a synthetic halogenated derivative of cortisol with mineralocorticoid effect. In addition, cortisol

and cortisone are naturally occurring corticosteroids which are also available in synthetic form. The mechanism of action of antiinflammatory activity of glucocorticoids is by suppression of synthesis and release of mediators including prostaglandins that initiate vascular changes as well as the immune response. Methylprednisolone, prednisolone, or prednisone are recommended for their strong antiinflammatory, antiallergic effects and low mineralocorticoid potency which limits the sodium and water retention when used chronically or in large doses. Hydrocortisone is commonly used for oral replacement therapy in adrenocortical insufficiency and fludrocortisone for replacing aldosterone in Addison's disease and chronic adrenal hyperplasia. The various preparations are equivalent in their anti-inflammatory and side effects profile provided equipotent doses are used; however, with varying propensity to cause fluid retention.[4,5] The comparative pharmacology of various available glucocorticoid and mineralocorticoid hormones are enlisted in Table 1.

Adverse Effects of Systemic Adrenal Steroid Pharmacotherapy

The adverse effects are the extension of the physiological and pharmacological actions of glucocorticoids and depends on the corticosteroid used, its dose, and the duration for which it is used. A short use of systemic corticosteroids (<7 days) even at high doses are unlikely to produce any adverse events. Inhaled and topical corticosteroids are least likely to produce any adverse effect.[4,5]

The important adverse effects of chronic glucocorticoid therapy are:

Gastrointestinal: Acute erosive gastritis and peptic ulcers are the problems with prolonged therapy. Intestinal perforation and pancreatitis have also been frequently reported with its use. The concomitant use of nonsteroidal antiinflammatory drugs further increases the complication rate.

Suppression of the inflammatory response: Immunosuppression and suppression of inflammatory response to infection is observed with chronic glucocorticoid therapy. This results in increasing incidence of infection, especially candidiasis, tuberculosis, pneumocystis carinii increases with steroid therapy.

Musculoskeletal: Proximal myopathy, tendon rupture, osteoporosis leading to vertebral collapse are reported with the prolonged use. In children, growth is impaired.

Metabolic effects: Chronic dosing leads to Cushing's syndrome: central obesity, moon face, striae, acne, hirsutism. Diabetes mellitus may occur. Some patients may also develop hyperlipidemia and hypophosphatemia. Preexisting diabetes is not a contraindication to glucocorticoid therapy. Hyperglycemia during the steroid therapy does not preclude the treatment for diabetes.

Central nervous system: Depression, psychosis, euphoria, insomnia, and epilepsy are the few adverse effects of steroid therapy.

Ophthalmic effects: Posterior subcapsular lens cataract, glaucoma, and corneal or scleral thinning are reported adverse effects when the dose exceeds prednisolone 10 mg/day or equivalent for more than a year.

Inhibition of HPA axis: Will be discussed in detail later.

Miscellaneous: These include delayed tissue healing, hypercoagulability of blood with thromboembolic complication, acne, hirsutism and paradoxically, hypersensitivity reactions.

Table 1: Comparative pharmacology of various corticosteroid preparations

Steroid	Glucocorticoid	Mineralocorticoid	Equivalent dose for oral and intravenous routes (mg)	Duration (h)	Elimination half life	Biologic half life
Short-acting						
Cortisol	1.0	1.0	20	8-12	1.5-3	8-12
Cortisone	0.8	0.8	25	8-12	0.5	
Aldosterone	0.3	3000	-	8-12		
Intermediate acing						
Prednisone	4.0	0.8	5	12-36	2-4	12-36
Prednisolone	4.0	0.8	5	12-36	2-4	
Methylprednisolone	5.0	0.5	4	12-36	2-4	
Fludrocortisone	10.0	125	-	12-36	-	
Long-acting						
Dexamethasone Betamethasone	25-40	0	0.75	>24	3.5-5.0	36-72
Paramethasone						

Adapted from Stoelting RK, Dierdorf SF. Endocrine disease. In: Stoelting RK. Ed. Anaesthesia and Co-existing Disease. New York, NY: Churchill Livingstone; 1993: 358

HPA Suppression and Perioperative "Stress Dose" of Steroids

The HPA axis consists of hypothalamus, pituitary, and adrenal glands. The hypothalamus secretes CRH in response to stress, circulating levels of cortisol, and sleep–wake cycle. The CRH then stimulates pituitary to release ACTH, which in return stimulates the adrenal cortex to release cortisol. Cortisol is a negative feedback inhibitor of both CRH and ACTH. It acts through various intracellular receptors to prevent the proliferation of T cells, counteract insulin by increasing gluconeogenesis, promote breakdown of lipids and protein, maintain vascular tone, and decrease bone formation.[4]

The chronic exogenous glucocorticoid is the common reason for the suppression of HPA axis causing adrenal suppression, and the concept of "perioperative exogenous corticosteroid" is based on this fact. Exogenous corticosteroids when given suppresses the normal diurnal rhythm as well stress associated increase in ACTH. This is especially seen when exogenous dose exceeds physiological levels. HPA axis suppression may persist for up to 1 year following the course of steroids.[6] As a result, the release of endogenous cortisol in response to surgical stress is absent or blunted. Clinical signs of adrenal insufficiency include hypotension, hypoglycemia, dehydration, and altered mental status: all are potentially fatal.[6] This is of particular relevance in the perioperative period warranting consideration in the differential diagnosis of refractory hypotension. The likelihood of HPA axis suppression following steroid therapy is determined by the dose and the duration of therapy. Therefore, larger the dose and more prolonged the duration, higher the chances of HPA axis suppression, thus, explaining why dexamethasone despite having highest antiinflammatory effects is not used for prolonged duration. To avoid HPA axis suppression, it is advisable to administer the minimum effective dose and alternate day therapy when appropriate. The risk of HPA axis suppression is low with topical and inhalational steroids. The factors determining HPA suppression with topical steroids are surface area of application, duration, occlusive dressing, drug potency. The factors determining HPA suppression with inhalational agents are dose, duration, and the potency of drug. Very commonly in our clinical practice, we encounter patients who are on budesonide inhalers. The bioequivalent dose of budesonide to 15 mg prednisone is 1.8 mg.[7] The bioequivalent doses of various steroid preparations to prednisolone are given in Table 2.

Table 2: The bioequivalent doses of various steroid preparations

Equivalency: Prednisone 10 mg is equivalent to
Betamethasone 1.5 mg
Cortisone acetate 50 mg
Dexamethasone 1.5 mg
Hydrocortisone 40 mg
Methylprednisolone 8 mg

For inhaled steroids: ≥750 mcg fluticasone or 1500 mcg beclomethasone/day, treat as ≥10 mg prednisolone/day

Need and Dose of Perioperative "Stress Dose" of Steroid

As far as the "stress dose" of steroid for replacement is concerned, typically, the supraphysiologic dose of 100 mg every 8 hourly had been in practice as replacement therapy for the last six decades.[2,8] A number of studies suggest that supplemental exogenous stress glucocorticoids may not be needed to meet the demands of perioperative stress.[9-14] However, all studies were either retrospective studies or had a small sample size. With further increased understanding of the physiologic stress responses and glucocorticoid, this regimen was questioned. Various trials have studied the supraphysiologic (ten times the normal production rate), physiologic (same as of normal production rate), and subphysiologic (one-tenth the dose of normal production rate) doses of steroids for replacement therapy. The data based on various animal and human trials have negated the role of "stress dose" of corticosteroids in patients on chronic steroid therapy.[9-12,15]

Friedman *et al.*[12] performed a prospective study on patients receiving immunosuppressive doses of glucocorticoids and undergoing major orthopedic operations. They observed that no patient developed clinical evidence of adrenocortical insufficiency despite being on their usual daily dose of glucocorticoid; in addition, despite receiving high adrenally suppressive dosages of glucocorticoids before surgery, 71% of the patients increased production of endogenous corticosteroid in response to surgical stress as measured by urinary level of free cortisol. Similarly, the outcomes of stress dose of steroids on renal- or pancreas/kidney-transplant recipients undergoing surgical lymphocele drainage were evaluated and no difference was observed in morbidity between the two groups, with none of the patients developing clinical evidence of adrenal insufficiency.[9]

Recently, two landmark studies have yet again refuted the role of "stress dose" of steroid in patients on chronic steroid therapy. One is a randomized trial of patients on chronic steroid therapy undergoing major colorectal surgery; no differences in postural hypotension or adrenal insufficiency were seen between those receiving high-dose glucocorticoids (hydrocortisone 100 mg intravenously three times daily) and low-dose glucocorticoids (the equivalent of their preoperative dose given intravenously).[16] Second was a retrospective cohort study of

patients with inflammatory bowel disease undergoing surgery and here too it was observed that administration of low-dose perioperative steroids (the equivalent of their preoperative dose given intravenously) did not lead to any incidence of hemodynamic instability requiring vasopressors or additional steroids for adrenal insufficiency perioperatively.[17]

Marik and Varon in a systematic review on perioperative stress dose of corticosteroid included nine studies with 315 patients and concluded that patients receiving therapeutic doses of corticosteroids who undergo a surgical procedure do not routinely require stress doses of corticosteroids so long as they continue to receive their usual daily dose of corticosteroid. In addition, they concluded that adrenal function testing is not required in these patients because the test is overly sensitive and does not predict which patient will develop an adrenal crisis. However, patients receiving physiologic replacement doses of corticosteroids owing to primary disease of the HPA axis must receive supplemental doses of corticosteroids in the perioperative period.[18] Yong *et al.* in their Cochrane review, which includes only 37 patients from two randomized controlled trials, suggested that supraphysiologic corticosteroid dosing is not necessary preoperatively to prevent adrenal insufficiency, but that current evidence is not adequate to fully support or refute this claim. They also concluded that it is likely that the majority of adrenally suppressed patients undergoing surgery, administration of the patient's daily maintenance dose of corticosteroid may be sufficient and that supplemental doses are not required.[14]

The considerations for steroid regimen include evaluation of equipotent dose of steroid causing HPA suppression and the duration for which patient is on steroid therapy. The onset of adrenal suppression can occur as early as 1 week after commencing therapy, and usually requires doses of 10 mg of prednisone equivalent or greater. Therefore, patients receiving "physiologic replacement" doses (<10 mg/day) do not need additional steroids perioperatively beyond their standard regimen. Patients receiving steroid in a dose of >10 mg/day, should receive "physiologic replacement" dose of steroid. Table 1 shows the equivalent doses of 10 mg prednisolone. Similar to the dose, the duration for which patient has stopped steroids is also an important determining factor for initiating steroid therapy in the perioperative period. If the patient had stopped steroids within the last 3 months, we must treat patient as if on steroids; whereas, if patient had stopped steroids more than 3 months back, no perioperative steroids are necessary. The consideration of the dose for supplemental stress doses depends on the basic understanding of endogenous cortisol production. Normal cortisol production on average is 15–20 mg/day, which can increase to 50 mg/day in response to minor procedures and 75–150 mg/day for moderate/major surgery.[19-21] Thus, a dose of 100 mg/day of exogenous cortisol or glucocorticoid should be sufficient to sustain hemodynamics even if the stress would cause ten-fold increase in cortisol production in case of endogenous HPA axis suppression.[22]

As far as the regimen for perioperative stress dose of steroids is concerned, there have been no universally accepted standard regimen. Most commonly used regimens are the ones from Salem *et al.*[2] and Nicholson *et al.*,[23] with a very slight difference between the two. Subsequently, Aker and Biddle[24] and Jabbour[25] gave intra and postoperative tapered steroid dose regimen. A rational regimen for steroid supplementation in the perioperative period is administration of cortisol 25 mg iv, at the induction of anesthesia followed by continuous infusion of cortisol 100 mg during the following 24 h [Table 3]. This approach maintains the plasma concentration of cortisol above normal during major surgery in patients receiving chronic treatment with steroids and manifesting a subnormal response to preoperative infusion of ACTH.[26] In addition to intravenous supplementation with cortisol, patients receiving daily maintenance doses of steroids should also receive this dose with premedication on the day of surgery. In those instances, such as burns or sepsis which exaggerate the need for exogenous steroid supplementation, continuous infusion of cortisol, 100 mg every 12 h is sufficient.[25]

An infusion of steroids is preferable as it avoids large increases caused by bolus injection. Owing to the practical limitations of the infusion, some studies have shown that daily dose of one-quarter administered every six hourly may be adequate.[26] Perioperative steroid supplementations may also be associated with rare complications such as aggravation of hypertension, fluid retention, inducement of stress ulcers, and psychiatric disturbances. The common complications include impaired wound healing and an increased rate of infection. The anesthetic considerations of patients on chronic steroid therapy include avoidance of use of etomidate; however, no specific anesthetic agent or technique is recommended in patients with/or at risk of adrenal insufficiency. The use of invasive monitoring, intraoperative IV corticosteroids,

Table 3: Suggested perioperative steroid regimen

Patients whose have received a regular daily dose of >10 mg prednisolone or equivalent in the last 3 months	
Minor surgery (hernias, hand surgery)	25 mg hydrocortisone at induction
Moderate surgery (hysterectomy)	Usual preoperative steroids + 25 mg hydrocortisone at induction + 100 mg hydrocortisone/day for 24 h
Major surgery (surgery where there is delayed oral intake, major trauma, prolonged surgery)	Usual preoperative steroids + 25 mg hydrocortisone at induction + 100 mg hydrocortisone/day for 2-3 days Resume normal oral therapy when gastrointestinal function has returned

All other patients - no additional steroids required

fluid and electrolyte resuscitation, and minimal doses of anesthetic agents must be considered in patients with adrenal insufficiency.

Conclusion

There are no dogmatic guidelines regarding perioperative "stress dose" of steroids in patients on chronic steroid therapy; however, there is enough evidence that patients on long-term exogenous steroid therapy do not require the conventional high-dose perioperative corticosteroid, instead must be kept on their baseline maintenance dose, i.e., 100 mg/day. In addition, a secondary adrenal insufficiency must be considered for any event of unexplained perioperative hypotension in these patients. There is a further need for high-quality randomized controlled trials in various surgical settings to evaluate the requirement for supplemental perioperative steroids in patients with preexisting primary adrenal insufficiency.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Fraser CG, Preuss FS, Bigford WD. Adrenal atrophy and irreversible shock associated with cortisone therapy. J Am Med Assoc 1952;149:1542-3.
2. Salem M, Tainsh RE Jr., Bromberg J, Loriaux DL, Chernow B. Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. Ann Surg 1994;219:416-25.
3. Lewis L, Robinson RF, Yee J, Hacker LA, Eisen G. Fatal adrenal cortical insufficiency precipitated by surgery during prolonged continuous cortisone treatment. Ann Intern Med 1953;39:116-26.
4. Schimmer BP, Funder JW. ACTH, adrenal steroids and pharmacology of the adrenal cortex. Goodman and Gilman's the Pharmacological Basis of Therapeutics. 12th ed. New York, NY: McGraw Hill; 2011.
5. Stewart PM, Krone NP. The Arenal cortex. Williams Textbook of Endocrinology. 12th ed. Philadelphia, PA: Saunders Elsevier; 2011.
6. Coursin DB, Wood KE. Corticosteroid supplementation for adrenal insufficiency. JAMA 2002;287:236-40.
7. Toogood JH, Baskerville J, Jennings B, Lefcoe NM, Johansson SA. Bioequivalent doses of budesonide and prednisone in moderate and severe asthma. J Allergy Clin Immunol 1989;84:688-700.
8. Shaw M, Mandell BF. Perioperative management of selected problems in patients with rheumatic diseases. Rheum Dis Clin North Am 1999;25:623-38, ix.
9. Mathis AS, Shah NK, Mulgaonkar S. Stress dose steroids in renal transplant patients undergoing lymphocele surgery. Transplant Proc 2004;36:3042-5.
10. Glowniak JV, Loriaux DL. A double-blind study of perioperative steroid requirements in secondary adrenal insufficiency. Surgery 1997;121:123-9.
11. Bromberg JS, Baliga P, Cofer JB, Rajagopalan PR, Friedman RJ. Stress steroids are not required for patients receiving a renal allograft and undergoing operation. J Am Coll Surg 1995;180:532-6.
12. Friedman RJ, Schiff CF, Bromberg JS. Use of supplemental steroids in patients having orthopaedic operations. J Bone Joint Surg Am 1995;77:1801-6.
13. Thomason JM, Girdler NM, Kendall-Taylor P, Wastell H, Weddel A, Seymour RA, *et al.* An investigation into the need for supplementary steroids in organ transplant patients undergoing gingival surgery. A double-blind, split-mouth, cross-over study. J Clin Periodontol 1999;26:577-82.
14. Yong SL, Coulthard P, Wrzosek A. Supplemental perioperative steroids for surgical patients with adrenal insufficiency. Cochrane Database Syst Rev 2012;12:CD005367.
15. Udelsman R, Ramp J, Gallucci WT, Gordon A, Lipford E, Norton JA, *et al.* Adaptation during surgical stress. A reevaluation of the role of glucocorticoids. J Clin Invest 1986;77:1377-81.
16. Zaghiyan K, Melmed GY, Berel D, Ovsepyan G, Murrell Z, Fleshner P, *et al.* A prospective, randomized, noninferiority trial of steroid dosing after major colorectal surgery. Ann Surg 2014;259:32-7.
17. Zaghiyan K, Melmed G, Murrell Z, Fleshner P. Safety and feasibility of using low-dose perioperative intravenous steroids in inflammatory bowel disease patients undergoing major colorectal surgery: A pilot study. Surgery 2012;152:158-63.
18. Marik PE, Varon J. Requirement of perioperative stress doses of corticosteroids: A systematic review of the literature. Arch Surg 2008;143:1222-6.
19. Brown CJ, Buie WD. Perioperative stress dose steroids: Do they make a difference? J Am Coll Surg 2001;193:678-86.
20. Siniscalchi A, Spedicato S, Dante A, Riganello I, Bernardi E, Pierucci E, *et al.* Fluid management of patients undergoing intestinal and multivisceral transplantation. Transplant Proc 2008;40:2031-2.
21. de Lange DW, Kars M. Perioperative glucocorticosteroid supplementation is not supported by evidence. Eur J Intern Med 2008; 19:461-7.
22. Kelly KN, Domajnko B. Perioperative stress dose of steroids. Clin Colon Rectal Surg 2013;26:163-7.
23. Nicholson G, Burrin JM, Hall GM. Peri-operative steroid supplementation. Anaesthesia 1998;53:1091-104.
24. Aker J, Biddle C. Adrenal glucocorticoid supplementation: Reconsidering medical dogma. Curr Rev Nurs Anesth 1999;22:91-8.
25. Jabbour SA. Steroids and the surgical patient. Med Clin North Am 2001;85:1311-7.
26. Kehlet H, Binder C. Alterations in distribution volume and biological half-life of cortisol during major surgery. J Clin Endocrinol Metab 1973;36:330-3.