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Surgery in patients on long-term steroid therapy: a tentative model for risk assessment

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Increased morbidity after operation has been associated with long-term steroid therapy. To determine the correlation between steroid therapy and such morbidity, the perioperative course of 55 steroid-treated patients was reviewed: 27 had bronchopulmonary disorders (group P) and 28 had non-pulmonary diseases (group NP). There were six (11 per cent) deaths, of which three were steroid related. Among the 13 non-lethal postoperative complications, eight were considered to be steroid related in group P and one in group NP. The duration of steroid therapy was for a median of 24 months (range 1–408 months) in group P and for a median of 6 months (range 1–240 months) in group NP (P < 0·01). In contrast, the daily dose of hydrocortisone or equivalent before operation was significantly lower in group P, with a median of 0·51 mg kg^{-1} day^{-1} (range 0·20–2·56 mg kg^{-1} day^{-1}) than in group NP, with a median of 1·20 mg kg^{-1} day^{-1} (range 0·23–7·38 mg kg^{-1} day^{-1}) (P < 0·01). In conclusion, bronchopulmonary disorders requiring a long duration of steroid therapy are associated with a higher risk of steroid-related complications after surgery. A convenient mathematical model is proposed which may allow a preoperative assessment of surgical risk, using steroid dose and duration of treatment.

Keywords: Obstructive lung disease, operative surgery, pituitary–adrenal system, probability, steroids

Long-term steroid therapy in surgical patients has been associated with an increased perioperative risk of developing complications related to inhibition of the hypothalamic–pituitary–adrenal axis. This inhibition causes not only an insufficient response to stress but also an impairment of tissue healing and a variety of endocrine and metabolic side-effects, including increased susceptibility to infection[1–3]. The physical status classification of the American Society of Anesthesiologists (ASA)[4], the Goldman cardiac risk index (CRI)[5] and the acute physiology score (APS)[6,7] do not include steroid therapy as a specific risk factor. Steroid impregnation and the related side-effects depend largely on dose and duration of therapy as well as on the nature and severity of the underlying disease. There is considerable individual variation. So far little has been written about the correlation between morbidity after surgery and the level of steroid impregnation.

This paper reviews a personal experience of postoperative complications in steroid-treated patients. A tentative model, using dose and duration of steroid therapy before operation as parameters of steroid impregnation, is proposed which may allow a convenient preoperative classification of surgical risk in such patients.

Patients and methods

Patients

Between February 1982 and December 1989, 55 steroid-treated patients had a total of 55 surgical procedures. There were 32 men and 23 women of mean(s.d.) age 57(17) years (median 61 years, range 21–87 years). Forty patients had intraperitoneal operations (splenectomy, seven; complicated duodenal ulcer surgery, four; cholecystectomy, five; Nissen fundoplication, one; ileal resection, four; colonic surgery, 17; Puestow procedure, two). Fifteen patients had extraperitoneal surgery (Patey mastectomy, one; thyroidectomy, two; umbilical or inguinal hernia, 11; radical nephrectomy, one). There were 24 (44%) emergency operations, nine of which were for acute complications related in part to steroid treatment (bleeding ulcer, three; perforated duodenal ulcer, one; sigmoid perforation, five). Seven operations were performed under spinal anaesthesia and 48 under general anaesthesia.

Steroid therapy

The indications for steroid treatment are detailed in *Table 1*. All 55 patients were receiving long-term steroids at the time of surgery; the median duration of therapy was 18 months (range 1–408 months). All patients received daily oral ($n=51$) or intravenous ($n=4$) steroids. Preoperative steroid dose was expressed as the daily dose of hydrocortisone, or the equivalent hydrocortisone dose if a synthetic analogue was used, during the last month before surgery. The median preoperative steroid dose was 51 mg day^{-1} (range 15–480 mg day^{-1}). Replacement therapy in primary chronic adrenal insufficiency or very short-term steroid treatment for conditions such as septic shock was not included in the study. The features of long-term steroid administration were present in many patients (Cushingoid appearance, 12; osteoporosis, 20; diffuse ecchymoses, 13; myopathy, eight; history of poor wound healing or susceptibility to infection, 14; peptic ulcer disease, ten; impaired glucose tolerance, 19).

Perioperative management

For elective surgery, attempts were made to reduce the preoperative steroid dose, especially in haematological disorders which were usually treated with short-term high-dose therapy. Elective patients had respiratory preparation with incentive spirometry[8]. Appropriate supplementary hydrocortisone hemisuccinate was given intramuscularly with premedication, and the same drug was used intravenously during and in the early period after surgery. The dose was gradually reduced within 2–7 days[3]. All patients received at least short-term prophylactic antibiotics. In some cases a 7–10-day course of antibiotics was justified. Precautions concerning the abdominal wound were taken, including interrupted absorbable aponeurotic sutures, an elastic abdominal girdle, and delayed removal of skin stitches (3 weeks). One author (L.A.M.) was involved with the operative and perioperative management of all patients.

Risk factor assessment

The preoperative condition of each patient was assessed using the ASA classification[4] and Goldman's CRI[5]. To analyse the steroid

Table 1 *Indications for long-term steroid administration in 55 patients*

Indication	*n*
Bronchopulmonary diseases (49%)	
Chronic obstructive airways disease	23
Atopic asthma	4
Haematological disorders (22%)	
Idiopathic thrombocytopenic purpura	6
Chronic lymphocytic leukaemia	4
Non-Hodgkin's lymphoma	1
Waldenström's macroglobulinaemia	1
Miscellaneous (29%)	
Regional enteritis (Crohn's disease)	6
Pemphigus vulgaris	1
Rheumatoid arthritis	7
Intracranial hypertension (metastatic carcinoma)	2

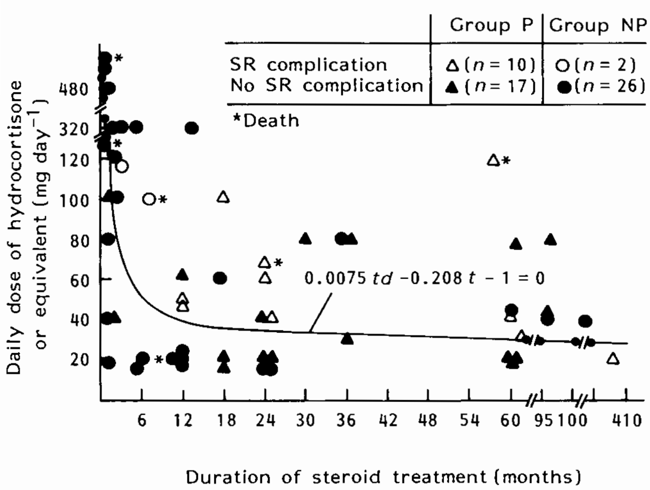

Figure 1 *Total duration (months) of steroid therapy*, t (x *axis*) versus *dose (mg day*$^{-1}$) *of hydrocortisone or equivalent during the last month before surgery*, d, (y *axis*). *The hyperbolic curve shows an estimated relationship between the variables* t *and* d *and is derived from the data of Kehlet and Binder*[9]. *SR, steroid-related*

impregnation of patients two parameters were used: total duration of steroid therapy in months (t) and daily dose of hydrocortisone in mg day^{-1} during the last month before surgery (d). Data from Kehlet and Binder[9] allowed a relationship to be derived between these variables t and d. The following is an equivalence equation of a hyperbolic curve[10]:

$$0{\cdot}0075td - 0{\cdot}208t - 1 = 0$$

According to this tentative mathematical relationship, each point on the curve corresponds to an equivalent steroid impregnation (*Figure 1*). Patients' data were plotted on the graph and location above (high impregnation) or below (low impregnation) the hyperbolic curve was recorded for subsequent analysis.

Steroid-related complications

Steroid-related complications after surgery were defined as: (1) an episode of adrenal insufficiency due to impairment of the hypothalamic–pituitary–adrenal axis; (2) problems due to altered tissue healing such as dehiscence, incisional hernia, hernia recurrence, etc., and those of increased tissue fragility and susceptibility to infection; (3) perioperative upset in steroid therapy leading to complications related to the underlying steroid-treated disease, especially bronchopulmonary disease.

Statistical analysis

Non-parametric methods were used: Wilcoxon's rank sum test for numerical variables and Fisher's exact test for categorical variables.

Results

Six of the 55 patients died, giving a hospital mortality rate of 11 per cent; three deaths were steroid related. All six died after emergency surgery for which the mortality rate was 25 per cent.

The first of the six patients who died after emergency operation was an 87-year-old woman, classified ASA IVE, CRI III, who had been treated for 10 months with oral steroids (preoperative dose 20 mg day^{-1} hydrocortisone) for a Waldenström's macroglobulinaemia. She was operated on for small bowel infarction and her death on the 36th day after surgery from heart failure was not considered to be related to steroid. The second and the third patients were, respectively, men aged 65 and 71 years, both classified ASA IIIE, CRI III, who had been treated for 7 months with oral steroids (mean preoperative dose 100 mg day^{-1}) for chronic lymphocytic leukaemia with severe thrombocytopenia. They were operated on for acute cholecystitis, with choledocholithiasis in one case and ischaemic colitis in the other. The latter patient died from septic shock. Peroperative haemostasis was particularly difficult owing to tissue friability, especially of the liver, in the patient with choledocholithiasis. This patient died on the first day after operation from intraperitoneal bleeding. This death was considered to be related to steroid. The fourth and fifth patients who died were, respectively, men aged 60 and 66 years who were admitted to the intensive care unit for carbon dioxide narcosis. Both were classified ASA IVE, CRI IV. They had been treated for 24 months with oral steroids (mean preoperative dose 60 mg day^{-1}) for severe chronic obstructive airways disease (COAD). They had subtotal gastrectomy to control massive haemorrhage from a bleeding duodenal ulcer and bleeding gastritis. They developed incisional hernia and were unable to be weaned from mechanical ventilation. As ventral hernia complicated the pulmonary problem, their deaths were considered to be steroid related. The sixth patient was a 68-year-old man who had ischaemic colitis after a cardiac arrest following carotid endarterectomy. This death was not considered to be steroid related.

Non-lethal postoperative complications were encountered in 13 patients. Nine were related to preoperative steroid treatment (*Table 2*). The only secondary adrenal insufficiency encountered after operation was in a 58-year-old man with COAD who had been treated with hydrocortisone (20 mg day^{-1}) for 34 years and operated on as an emergency for acute faecal peritonitis from perforated diverticulitis. Peritoneal lavage and Hartmann's procedure were performed under general anaesthesia with 65 mg supplementary intravenous methylprednisolone. The parenteral steroid dose was reduced gradually during the first week after surgery and was replaced by 20 mg day^{-1} oral prednisolone on day nine. Subsequently, the patient insidiously developed lethargy, weakness, orthostatic hypotension and a mild hyperkalaemia up to 5·3 mmol/l. A short tetracosactrin stimulation test using 250 μg Synacthen® (Ciba Laboratories, Horsham, UK) showed no response of plasma cortisol and confirmed adrenocortical insufficiency which was reversed by supplementary oral steroid.

Four of the 13 non-lethal complications were not considered to be related to preoperative steroid impregnation: lymphatic fluid collection in the axilla after radical modified mastectomy (one case), deep femoral thrombosis 15 days after inguinal herniorraphy (two cases), and paralytic ileus following exploratory laparotomy in a patient with cerebral metastatic tumour.

No correlation could be found between the rate of steroid-related complications and the presence of clinical features of long-term steroid administration. In view of the high incidence of postoperative steroid-related morbidity in patients with bronchopulmonary disorders, a comparative study of two subpopulations was performed: group P (pulmonary disease as indication for steroid therapy, $n = 27$) and group NP (non-pulmonary disorder, $n = 28$). *Table 3* shows that while steroid dose was significantly lower in group P, duration of therapy was longer. Meaningful comparison of morbidity rates between group P and group NP was possible as the groups were comparable for age, sex, preoperative risk scores (ASA, CRI), type of surgery (intraperitoneal or extraperitoneal procedures) and number of emergency procedures. The

Table 2 *Clinical data of nine patients who developed non-lethal steroid-related complications*

Age (years)	Sex	Disease	Steroid therapy before operation: Duration (months)	Steroid therapy before operation: Hydrocortisone dose (mg day^{-1})	ASA*	CRI†	Type of operation	Steroid-related morbidity after operation
60	M	COAD	24	40	IVE	III	Suture of duodenal ulcer +omentoplasty	Recurrent pneumothorax
58	M	COAD	408	20	IIIE	II	Hartmann's procedure for perforated diverticulitis	Adrenal insufficiency
68	M	COAD	12	50	III	I	Right colectomy for adenocarcinoma	Evisceration
33	F	Atopic asthma	24	60	IIE	I	Bassini's procedure for strangulated inguinal hernia	Relapse of inguinal hernia with crural strangulated hernia
57	F	COAD	60	40	IIIE	I	Repair of umbilical hernia	Severe bronchospasm after extubation
65	F	COAD	18	100	IV	III	Puestow's procedure	Acute respiratory distress syndrome
71	M	COAD	61	30	IIIE	II	Repair of iatrogenic colonic perforation	Wound abscess and subsequent incisional hernia
86	M	COAD	12	48	IVE	IV	Hartmann's procedure for perforated diverticulitis	Wound sepsis and incisional hernia
30	F	Crohn's disease	2	150	III	II	Right colectomy	Wound sepsis

* American Society of Anesthesiologists' physical status[4]; † cardiac risk index of Goldman *et al.*[5]; COAD, chronic obstructive airways disease

Table 3 *Comparison of surgical patients with pulmonary (P) or non-pulmonary (NP) underlying diseases*

	P ($n=27$)	NP ($n=28$)	*P*
Median (range) steroid dose* (mg day^{-1})	20 (15–100)	80 (20–480)	<0·01
Median (range) steroid dose (mg kg^{-1} day^{-1})	0·51 (0·20–2·56)	1·20 (0·23–7·38)	<0·01
Median (range) duration of steroid therapy (months)	24 (1–408)	6 (1–240)	<0·01
ASA† (>III/≤III)	17/10	14/14	n.s.
CRI‡ (>II/≤II)	14/13	12/16	n.s.
Emergency/elective surgery	11/16	13/15	n.s.
Steroid-related postoperative complications	10 (37%)	2 (7%)	0·016
Non-lethal steroid-related postoperative complications	8 (33%)	1 (4%)	0·037

* Steroid doses are expressed in mg day^{-1} hydrocortisone or equivalent; † American Society of Anesthesiologists' physical status[4]; ‡ cardiac risk index, Goldman *et al.*[5]; n.s., not significant

morbidity rate was significantly greater in group P than in group NP.

The parameters of preoperative steroid therapy for each individual patient were plotted on the dose–duration graph (*Figure 1*). Eleven (34 per cent) of the 32 patients located above the derived equivalence curve developed steroid-related complications after operation, from which some died, compared with only one of the 23 patients located below the curve ($P=0·014$). Nine out of sixteen patients from group P who were located above the curve developed steroid-related complications compared with two out of 16 patients from group NP who were similarly located above the curve ($P=0·023$). This rate of 56 per cent for postoperative complications in patients on steroids for severe bronchopulmonary disorders was markedly higher than the rate of 12 per cent experienced in 520 general surgical patients with COAD who did not require steroid treatment. Furthermore, of the 23 patients located below the curve, 11 were in group P and only one (9 per cent) developed a steroid-related complication. The total rate of postoperative dehiscence or incisional hernia occurrence after intraperitoneal surgery was 13 per cent (five out of 40 patients), and the rate of recurrence after hernia repair was 9 per cent (one out of 11 patients). During the study period the rate of incisional hernia occurrence after abdominal surgery in 1580 patients, and of recurrence after hernia repair in 380 patients, was 2 per cent in those not treated with steroid.

Discussion

Assessment of operative risk classically includes the ASA[4] or CRI[5] scores. This particular population of chronically steroid-treated patients presented increased operative risk due to age, high ASA (>III in 56 per cent) and CRI (>II in 47 per cent) scores, high rate of emergency surgery, and severity of the steroid-treated underlying disease. Therefore, operative morbidity and mortality rates were expected to be high[5–11]. However, the specific adverse effects of preoperative steroid therapy are hard to discriminate from the other associated risk factors[12,13]. Steroid therapy is not even taken into account in determining the ASA, CRI or APS[4–6]. Nevertheless, steroid treatment was considered recently to constitute a risk factor independent of the acute physiology and chronic health evaluation (APACHE II) for abdominal sepsis and related mortality[7]. However, the nature of the underlying disease and the amount of steroid impregnation were not considered in this work, since neither duration nor dose was analysed[7]. In the present series, patients with bronchopulmonary disorders had a significantly higher rate of postoperative steroid-related complications, and this correlated with long duration with low-dose preoperative steroid. This indicates the particular relevance of duration of therapy when assessing steroid-related operative risk.

Adrenocortical function, measured by repeated plasma corticosteroid estimation, was studied by Kehlet and Binder[9] in chronically steroid-treated patients undergoing major surgical procedures without supplementary hormone administration. In that study all patients who received 12·5 mg prednisone or more for over 6 months, 10 mg or more for over 2 years, or 7·5 mg or more for over 5 years showed an impaired adrenocortical response to surgery. These doses are essentially physiological replacement regimens[14]. Repeating such a study further to assess adrenocortical function and clinical course would have been unethical and so the proposed equivalence equation was calculated[10] using the cutting points from the histogram provided by Kehlet and Binder. The equation, which is that of a hyperbolic curve, allowed an easy classification of patients according to their level of steroid impregnation (above or below the physiological dose). Data of patients located above or below the curve correspond respectively to high or low steroid impregnation. Therefore, as this model reflects, the level of steroid impregnation, albeit imperfectly, may allow further discrimination between high and low steroid-related post-operative complication risk. This is strongly suggested by the data presented in this paper. Such a mathematical approach seems as justified as the simple compilation of signs or symptoms of exogenous hyperadrenocorticism, inasmuch as some patients receiving therapeutic doses of steroids develop Cushingoid changes whereas others receiving comparable doses do not. For instance the tendency of a given dose to cause Cushingoid changes is exaggerated if hypothyroidism or liver disease is present.

Although these results need further assessment in larger, prospective series, it appears that steroid prescribed for pulmonary disorders constitutes a potentially higher risk of complication than steroid prescribed for non-pulmonary disorders. For example, a patient with COAD receiving 15 mg methylprednisolone for more than 1 year presents a higher risk of complication than a patient with idiopathic thrombocytopenic purpura receiving 60 mg methylprednisolone for 2 months. Both patients have received steroid doses large enough to produce part or all of the syndrome of exogenous hyperadrenocorticism. Whether the complication is directly or indirectly related to steroid therapy is difficult to ascertain. For instance, dehiscence may be due to aggressive physical and respiratory therapy while postoperative pneumonia may be due to pusillanimous respiratory therapy through fear of causing incisional hernia. Nevertheless the complication rate of 56 per cent in COAD patients receiving steroid was dramatically higher than that of 12 per cent in general surgical COAD patients who did not take steroid. This reflects the contribution of steroid therapy to morbidity in patients with pulmonary disease.

In conclusion, this study reviewed 55 chronically steroid-treated patients undergoing surgical procedures. The probability of developing steroid-related complications after operation was higher in patients with COAD for which they required steroid therapy. The duration of steroid therapy in this subpopulation was longer than that in patients without pulmonary disease. The amount of steroid impregnation and the nature of the underlying disease for which steroid is administered should be considered together when assessing the risk of steroid-related complications.

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