The effect of chronic steroid therapy on outcomes following cardiac surgery: a propensity-matched analysis

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Abstract

Objective: Steroids are beneficial in reducing the inflammatory response accompanying surgery with cardiopulmonary bypass. However, chronic steroid therapy has been implicated as a risk factor for abdominal complications and mortality following surgery. We assessed the impact of chronic steroid therapy had on outcome following cardiac surgery.

Methods: During the period January 1999 to March 2003 there were 98 patients on chronic steroid therapy (Group S) who underwent cardiac surgery at our institution. These patients were matched with a control group of 98 patients who were not on steroids (Group C). A propensity score was used to perform the matching. The \(C\) statistic for this model was 0.72.

Results: Ninety (93.7\%) of the 98 patients in Group S had been on oral prednisolone for a median of 9.5 years (25th and 75th percentile of 5 and 12 years) with a median dose of 5 mg (25th and 75th percentile of 4 and 8.75 mg). Preoperative characteristics were well matched between both groups. There was no difference in the post-operative outcome between the two groups with respect to mortality, stroke, renal failure, abdominal complications, wound infections, requirement for inotropic support and myocardial infarction. Patients in Group S were more likely to develop atrial arrhythmias and to require prolonged ventilation, although this did not reach statistical significance.

Conclusions: Chronic steroid therapy was not associated with increased mortality or overall morbidity following cardiac surgery. However, patients on chronic steroids may be at greater risk of developing atrial arrhythmias or of requiring prolonged ventilation.

Keywords: Cardiac surgery; Steroids; Mortality; Morbidity

1. Introduction

Steroids provide benefits by decreasing the inflammatory response to stress. However, chronic steroid therapy causes an inhibition of the hypothalamic-pituitary-adrenal axis, resulting in an inadequate response to stress. This effect can be detrimental to the surgical patient. Chronic steroid use can also cause impairment in tissue healing, increase susceptibility to infection and lead to other endocrine and metabolic deregulation \cite{1,2}.

Chronic steroid therapy has also been implicated as a cause of increased abdominal complications following cardiac surgery \cite{3}. The Society of Thoracic Surgeons (STS) national adult cardiac surgery database \cite{4} also lists steroid therapy as a risk factor for increased mortality following cardiac surgery. However, the influence of chronic steroid therapy on the outcomes following cardiac surgery is not clear because the issue has never been adequately addressed.

We used a propensity-matched model to assess the influence of chronic steroid therapy has on morbidity and mortality following cardiac surgery.

2. Methods

2.1. Patient population and data

Between 1st January 1999 and 31st March 2003, a total of 6471 patients underwent cardiac surgery at our institution. Out of this total, 98 patients (1.5\%) were on chronic steroid therapy (Group S). These patients were matched with a control group (Group C) of 98 patients who were not on steroids (see Section 2.4).

Definitions and data collection methods are available from www.nwheartaudit.nhs.uk. Data was collected prospectively during the patient's admission as part of routine clinical practice on the variables listed in Table 1 (pre-operative) and Table 2 (in-hospital outcomes), including the type of cardiac operation performed.

In-hospital mortality was defined as death within the same hospital admission. Re-exploration for bleeding was defined as bleeding that required surgical re-operation after initial departure from the operating theatre. Post-operative
stroke was defined as a new focal neurological deficit or comatose state that occurred post-operatively that persisted for more than 24 h after its onset and was noted before discharge. Confused states, transient neurological events and intellectual impairment were excluded from our study to avoid any subjective bias. Renal failure was defined as patients not previously known to have renal failure who developed a serum creatinine greater than 200 μmol/L or who required new post-operative dialysis support. Post-operative myocardial infarction was defined as new Q-wave occurrence post-operation in two or more contiguous leads on an electrocardiogram or a significant rise in post-operative creatinine kinase MB isoenzyme. Post-operative ventricular arrhythmia was defined as the occurrence of new ventricular arrhythmia in the absence of preoperative ventricular arrhythmias. Gas-trointestinal complications included gastrointestinal bleeding, pancreatitis, ischaemic bowel and perforation, and were defined in accordance with the definitions of The Society of Cardiothoracic Surgeons of Great Britain and Ireland minimum dataset [6].

2.2. One-year survival

Patient records were linked to the National Strategic Tracing Service (NSTS) that records all deaths in the United Kingdom. To establish current vital status at 1 year, patients were matched to the NSTS based on patient name, National Health Service number, date of birth, gender, and postcode. One-year follow-up was complete.

2.3. Steroid therapy

In this study, chronic steroid therapy was defined as uninterrupted steroid therapy for a period of at least 90 days at a daily prednisolone dose of 5 mg or more, or equivalent for alternative steroid formulations. This definition was chosen because, despite the small dose of the prednisolone, there is a sufficient depression of the hypothalamic-pituitary-adrenal axis [7] for these patients to require supplemental doses of steroids during and after surgery.

2.4. Statistical methods

A propensity score was used to match steroid users with unique non-steroid users. Logistic regression was used to develop the propensity score which was constructed from core characteristics from all patients who underwent cardiac surgery during the study time period [8] and the type of operation. These variables are listed in Table 1. The C statistic for this model was 0.72. Steroid users were matched with non-steroid users who had an identical five-digit propensity score. If this could not be done, we then proceeded to a four-, three-, two-, or one-digit match [9]. Continuous variables are shown as median with 25th and 75th percentiles, and categorical variables are shown as a percentage. Comparisons were made with Wilcoxon rank-sum tests and Chi-square tests as appropriate. Deaths occurring as a function of time are described using Kaplan–Meier survival curves [10]. In all cases, a P value of less than 0.05 was considered statistically significant. All analyses were performed retrospectively with SAS for Windows Version 8.2.

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The commonest indication for chronic steroid therapy was polymyalgia rheumatica (58.2%), this was followed by connective tissue disorders, including systemic lupus erythematosi, rheumatoid arthritis and polyarteritis nodosa (11.2%) and asthma (10.2%). The indication for steroid therapy could not be ascertained in three patients (Table 3).

Both Group S and Group C were well matched with respect to preoperative variables (Table 1). Although not of statistical significance, Group S patients may have been more likely to suffer from diabetes mellitus ($P = 0.081$) and hypertension ($P = 0.063$). The different cardiac operations performed in the propensity-matched groups are shown in Fig. 1.

There were no statistical differences between the groups (Table 2) with respect to hospital mortality. Of the three steroid patients who died in-hospital, all received prednisolone for between 5 and 11 years, with two patients on 5 mg and one patient on 7.5 mg. Table 2 also shows that no statistical differences existed with respect to post-operative stroke, post-operative renal failure, ventricular arrhythmias, post-operative myocardial infarction, sternal wound infection, gastrointestinal complications, need for intra-aortic balloon pump, need for ionotropic support, length of stay in the intensive care unit, and the duration of hospital stay following surgery.

<table>
<thead>
<tr>
<th>Indication for steroid therapy</th>
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<tbody>
<tr>
<td>Polymyalgia rheumatica</td>
<td>57</td>
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<tr>
<td>Connective tissue disorders</td>
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<tr>
<td>Asthma</td>
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<tr>
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<tr>
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<tr>
<td>Myelodysplasia</td>
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</tr>
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A median of 9.5 years (25th and 75th percentiles: 5–12). The median daily prednisolone dose was 5 mg (25th and 75th percentiles: 4–8.75). Four patients were on a combination of cortisone and fludrocortisone because they suffered from adrenal failure and three patients were on hydrocortisone therapy for the management of asthma. One patient was on cortisone and fludrocortisone for membranous nephropathy.

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Ten (5.1%) deaths occurred during the 1-year follow-up period. The numbers of patients at risk at 1 year was 92 for Group S and 94 for Group C. Freedom from death (Fig. 2) in Group S at 30 days was 96.9%, and at 1 year was 97.9% and for Group C was 97.9% and 95.9%, respectively ($P = 0.51$).

Twenty-four patients were on 10 mg or more of prednisolone and all were alive at 1 year of follow-up. With respect to in-hospital outcomes (numbers are not mutually exclusive), two developed renal failure, nine developed atrial arrhythmias, one had a myocardial infarction, one developed a deep sternal wound infection, 10 were on inotropes, one had an intra-aortic balloon pump inserted, and three were ventilated for more than 24 h. No incidence of re-exploration for bleeding, stroke, gastrointestinal complications, or ventricular arrhythmia were recorded. All results were comparable to patients who received less than 10 mg of prednisolone.

4. Discussion

The quality and safety of cardiac surgery has attracted much attention and scrutiny from the media and the public. As such, hospitals are increasingly using risk stratified data to monitor surgical performance. However, it is imperative for accurate risk stratification that the influence of risk factors

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**Fig. 1.** Propensity-matched cardiac operations. CABG, coronary artery bypass grafting.

![Graph](https://example.com/fig1.png)

**Fig. 2.** Observed 1-year survival in propensity-matched groups. Number at risk at 30 days and 1 year for Group C were 96 and 94, and Group S were 95 and 92, respectively.

Group S patients appeared to have a higher incidence of atrial arrhythmias and a longer duration of post-operative ventilation, although these results did not reach statistical significance. It also appeared that the development of atrial arrhythmias was dependent on the total duration of steroid therapy. Group S patients who developed atrial arrhythmias had a median duration on steroid therapy of 11 years (25th and 75th percentiles: 6-14) compared to 7 years (25th and 75th percentiles: 3.5-11.5) for those who did not develop atrial arrhythmias ($P = 0.05$). The duration of steroid therapy did not affect the duration of ventilation and the daily steroid dosage was not significantly different with respect to atrial arrhythmia or duration of ventilation.

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on outcomes of cardiac surgery are continuously monitored as well.

The STS National Cardiac Surgery Database [4,11] lists steroid therapy as a risk factor for increased mortality in cardiac surgical patients with a relative risk of 2.36 for patients undergoing AVR, 1.89 for isolated CABG and 1.74 for MVR. In this study, the mortality in Group S was 3.1% compared to 2.0% in Group C and there was no statistical difference between the two groups (P = 0.65). A high level steroid dose also appeared to have no increased risk with all our patients with a steroid dose of 10 mg prednisolone or more were alive at 1-year follow-up.

Spotnitz et al. [3] have reported a relative risk of abdominal complications (relative risk of 6.3) in patients undergoing cardiac surgery while on steroid therapy. These patients were particularly prone to gastrointestinal bleeds and pancreatitis. Because of the paucity of literature on the outcome of patients on steroid therapy undergoing cardiac surgery, evidence of the influence in patients undergoing general surgical procedures was reviewed. There is an abundance of literature on the subject, but the evidence is inconclusive. Some reports show a dose-dependent increase in the incidence of gastrointestinal bleeds, peptic perforations, impaired healing of anastamoses with the attendant sequelae [12–14], while other reports show no influence regardless of the dose [15]. The disparity may be due to differences in patient selection, improvements in the technical aspects of surgery and anaesthesia and improved anti-ulcer prophylaxis [16]. In this study, there was no difference in the incidence of gastrointestinal complications between the groups. Our results compare well with the literature range of 0.3–2.3% [3].

There was no difference between the groups with respect to the incidence of deep sternal wound infection. While it has been shown that steroid therapy can predispose to prolonged hospital stay, wound infection, and bronchopneumonia [3,17] following general surgery, studies in cardiac patients [5,18] have not shown an association. Connective tissue disorders and high preoperative blood glucose levels have been shown to be independent risk factors for deep sternal wound infection. More than half of the patients in Group S had connective tissue disorders and steroid induced diabetes, yet the incidence of infections was the same as that of the Group C. The results compared well with the literature range of 0.2–2.3% [18].

Chronic steroid therapy does not appear to be a risk factor for stroke [19], renal impairment [20], increased need for inotropes or prolonged hospital stay [21]. The current study demonstrates no association between steroid therapy and these conditions.

A direct association between steroid therapy and prolonged ventilation has not been reported. However, an indirect association may be possible as patients with COPD or impaired preoperative pulmonary function are risk factors for prolonged mechanical ventilation after cardiac surgery [22,23]. Patients with COPD accounted for just about 5% of the propensity-matched population. The two groups of patients were comparable with respect to preoperative pulmonary function. The tendency for prolonged ventilation in the study group therefore, maybe, related to steroid therapy and needs to be investigated further.

Atrial Fibrillattion is an uncommon but recognised complication in patients with connective tissue disorders, particularly systemic lupus erythematosus and is secondary to associated pancarditis and coronary vasculitis [24]. Patients on steroid therapy for connective tissue disorders have been reported to be prone to arrhythmias although the pathogenesis of this association is not well understood [25]. This may explain the tendency for patients in our study, which included a significant number of patients with connective tissue disorders, to develop arrhythmias. Interestingly, the anti-inflammatory effects of short-term steroid therapy have been shown to benefit patients undergoing surgery for atrial arrythmias by reducing post-operative carditis and thus minimising the chance of recurrence [1]. Therefore, suffice to say that this interesting but relatively unexplored aspect of steroid induced complication needs further study and investigation before further conclusions can be drawn.

There are several limitations which need to be discussed which could affect the conclusions from this study. Firstly, a variety of definitions of chronic steroid therapy exist. While most studies have used dosage of steroids at the time of surgery to distinguish between high and low steroid doses [13–15], Reding et al. [2] have stressed the importance of considering both the dose and the duration of treatment in determining the chronicity of steroid therapy which the authors believe is the single most important consideration in the development of steroid related complications. They base their observations on the findings of Kehlet and Binder [7] who measured adrenocortical function in patients undergoing surgery and demonstrated an impaired adrenocortical response to surgery in patients receiving 12.5 mg prednisolone or more for at least 6 months, 10 mg or more for at least 2 years or 7.5 mg or more for at least 5 years. These doses essentially indicate the chronicity of steroid therapy required to suppress the hypothalamic-pituitary axis (HPA). In this study, the median prednisolone (or its equivalent) dosage on admission was 5 mg, which is arguably a low dosage. The lack of significant differences in outcomes between the groups may be attributed to this. However, if one were to consider the nomogram of Kehlet and Binder, the fact that the patients in this study were on steroid therapy for a median duration of 9.5 years would represent a level of chronicity of steroid therapy, sufficient to suppress the HPA axis and thus influence the incidence of complications. Also, examination of the outcomes of the 24 patients who received 10 mg or more of prednisolone did not reveal any trends to suggest an increased risk with a higher dose of steroid, with all surviving up to 1 year of follow-up. Secondly, the presence of coexisting diseases may have affected the results. Patients in Group S were on steroid therapy for a diverse set of pathological processes which by themselves may act independently in affecting the outcome following cardiac surgery. The small numbers of patients with these conditions prevented statistical analysis. Propensity matching allowed the effect of steroid therapy on two similar groups of patients to be compared; thus, the impact of co-existant disease was minimised. The possibility also exists that patients on steroids were identified early as being at risk and a policy of greater vigilance in the post-operative period and more aggressive management of
complications was adopted. Thirdly, this retrospective analysis of prospectively collected data has all of the attendant restrictions of any such study. Finally, the small sample size available to us, with only 98 steroid patients receiving cardiac surgery over a 5-year period, leaves the study vulnerable to type-II errors, especially when examining the impact of steroid dose on outcomes.

We conclude that given the limitations of this study, chronic steroid therapy may not constitute a increased risk for mortality or poorer outcome in patients undergoing cardiac surgery. Patients on steroid therapy may, however, require longer periods of mechanical ventilation and be more likely to suffer from atrial arrhythmias. Further research is needed to understand the potential effect of steroid therapy on atrial arrhythmia.

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