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Systematic review article

The impact of preoperative corticosteroids on the systemic inflammatory response and postoperative complications following surgery for gastrointestinal cancer: A systematic review and meta-analysis

Stephen T. McSorley*, Paul G. Horgan, Donald C. McMillan

Academic Unit of Surgery, School of Medicine, University of Glasgow, Glasgow, UK

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ABSTRACT

Background: This meta-analysis examined the impact of preoperative corticosteroids on interleukin 6 (IL-6), C-reactive protein (CRP), and complications following surgery for gastrointestinal cancer.
Methods: A systematic review was performed using appropriate keywords. Random-effects meta-analysis was performed.
Results: 11 RCTs with 474 patients, were included. Corticosteroids were significantly associated with lower IL-6 on postoperative day 1 (mean difference −148 pg/mL, 95% CI −205 to −92, $p < 0.001$), 2 (−33 pg/mL, 95% CI −58 to −8, $p = 0.01$), and 3 (−31 pg/mL, 95% CI −52 to −11, $p = 0.002$), lower CRP on day 3 (−45 mg/L, 95% CI −68 to −21, $p < 0.001$), and 7 (−14 mg/L, 95% CI −27 to −1, $p = 0.04$), and fewer postoperative infective complications (OR 0.47, 95% CI 0.26–0.83, $p = 0.01$).
Conclusion: Corticosteroids were associated with reduction in the postoperative systemic inflammatory response and complications following surgery for gastrointestinal cancer.

* Corresponding author at: Academic Unit of Surgery, R2.65, School of Medicine, University of Glasgow, New Lister Building, Glasgow Royal Infirmary, 10-16 Alexandra Parade, Glasgow G31 2ER, UK.
E-mail address: s.mcsorley@doctors.org.uk (S.T. McSorley).

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1. Introduction

Surgery leads to a predictable metabolic, neuroendocrine and immunological response (Cuthbertson, 1979; Marik and Flemmer, 2012). Activation of the sympathetic nervous system leads to the release of catecholamines which induce tachycardia, hypertension and tachypnoea (Desborough, 2000). The cellular response to surgical trauma involves the production of pro-inflammatory cytokines including tumour necrosis factor (TNF) alpha, interleukin (IL) 1, IL-6, and IL-8 (Baigrie et al., 1992; Dinarello et al., 2013). Such cytokines act to mobilise the innate immune system, resulting in the activation of neutrophils, macrophages and platelets, causing fever and contributing to nausea. Circulating pro-inflammatory cytokines also act on hepatocytes, altering the synthesis of the acute phase proteins, such as C-reactive protein (CRP), albumin, fibrinogen and constituents of the complement cascade (Gabay and Kushner, 1999).

Postoperative IL-6 and CRP concentrations in particular, have been found to be useful markers of the magnitude of the surgical injury (Watt et al., 2014). The magnitude of this postoperative systemic inflammatory response, and in particular the routinely available CRP, is associated with the development of complications following colorectal surgery, oesophagectomy and liver resection (Dutta et al., 2011; Platt et al., 2012; Adamina et al., 2015). Furthermore, threshold concentrations of CRP have been established, in the postoperative period, (190 mg/L on postoperative day 2, 170 mg/L on postoperative day 3 and 145 mg/L on postoperative day 4), which predict the likelihood of developing or not developing infective complications and anastomotic leak (Ramanathan et al., 2013; Singh et al., 2014a).

The magnitude of this postoperative systemic inflammatory response and its relationship with postoperative complications is of particular interest in the context of surgery for gastrointestinal cancers. Previous studies have demonstrated an association between postoperative complications, particularly infective complications, and poorer long-term and oncologic outcomes following surgery for gastrointestinal cancer (Mirnezami et al., 2011; Artinyan et al., 2015). Indeed, it has been suggested that the magnitude of the postoperative systemic inflammatory response should prompt further investigation to exclude the development of a postoperative infective complication (Warschkow et al., 2012). Furthermore, the upcoming PRECious trial (NCT02102217) aims to randomize patients to early CT imaging or standard postoperative care if CRP rises above 140 mg/L on postoperative day 3–5 following abdominal surgery (Straatman and van der Peet, 2015).

Given the relationship between the magnitude of the postoperative systemic inflammatory response, the development of postoperative complications, and long-term outcomes, there is increasing interest in the attenuation of this postoperative stress response. Preoperative corticosteroids are a logical choice of intervention given their potential potency and duration of effect (Sapolsky et al., 2000; Holte and Kehlet, 2002). Indeed, preoperative corticosteroids have been used as they have been found to reduce postoperative nausea and vomiting and analgesic requirements following abdominal surgery (Karanicolas et al., 2008; Waldron et al., 2013). A recent meta-analysis reported that preoperative corticosteroids significantly reduced postoperative day one IL-6, postoperative complications, infective complications, and length of stay following abdominal surgery (Srinivasa et al., 2011). Preoperative corticosteroids have also been reported to reduce postoperative IL-6 and complication rates following liver resection and oesophagectomy in meta-analyses of small numbers of studies (Richardson et al., 2014; Raimondi et al., 2006; Gao et al., 2014). To our knowledge, no prior meta-analysis has investigated comprehensively the impact of preoperative corticosteroids on the postoperative surgical stress response following surgery for gastrointestinal cancer. The present meta-analysis is the first to examine their impact on CRP. Both IL-6 and CRP are objective measures of the magnitude of the systemic inflammatory response to surgery, however CRP is more readily available in the clinical setting (Watt et al., 2014). Furthermore, no meta-analysis has attempted to assess the dose response between preoperative corticosteroids and the magnitude of the postoperative systemic inflammatory response and postoperative complication rate.

Therefore the objective of the present systematic review and meta-analysis was to examine the impact of preoperative corticosteroids compared to placebo in the context of randomized controlled trials, on the surgical stress response, in particular postoperative IL 6 and CRP, and their relationship with the development of infective complications, following surgery for gastrointestinal cancers.

2. Methods

The present systematic review and meta-analysis was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary Digital Content 1—PRISMA Checklist.docx) (Moher et al., 2010).

2.1. Outcomes of interest

The primary outcome of interest was the impact of single dose preoperative corticosteroids on markers of the postoperative stress response following surgery for gastrointestinal cancer, in particular IL-6 and CRP. Those studies reporting chronic preoperative corticosteroid use or dosing at other perioperative time points were excluded. Secondary outcomes included the impact of preoperative corticosteroids on postoperative complications, infective complications, and anastomotic leak following surgery for gastrointestinal cancer, including pre-specified subgroup analysis based on surgical speciality/site. Postoperative complications were coded as categorised by the authors of the included studies where possible. Where there was doubt the authors of the present study categorised complications using a schemata described previously (McSorley et al., 2015a). Post hoc meta-regression of the impact of corticosteroid dose on postoperative day 1 IL-6 was performed following completion of the pre-specified analyses. Study selection and data extraction was performed by one author (SM) and any uncertainties resolved by consensus discussion with the senior authors (PH, DM).

2.2. Literature search and study selection

A systematic literature review was performed of the US National Library of Medicine (MEDLINE), PubMed, and the Cochrane