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Original Research Paper

General Surgery

CORTICOSTEROID THERAPY FOR SEVERE ACUTE PANCREATITIS: A META-ANALYSIS OF RANDOMIZED, CONTROLLED TRIALS

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ABSTRACT **Background:** Recent reports about the benefits of corticosteroid therapy in patients with severe acute pancreatitis (SAP) have shown conflicting results. We aimed to explore the effects of corticosteroid therapy in SAP patients on patient outcomes by performing a meta-analysis. **Methods:** Databases (Medline, EMBASE, Web of Science, PubMed, Cochrane Library, Chinese Biomedicine Database, and China Academic Journal Full-Text Database) were queried for all relevant, randomized, controlled trials investigating corticosteroid therapy in patients with SAP. **Results:** Six randomized, controlled trials including 430 SAP patients were identified. Corticosteroid therapy for SAP was associated with reductions in the length of hospital stay, the need for surgical intervention, and the mortality rate (weighted mean difference [WMD]: -9.47, 95% confidence interval [CI]: -16.91 to -2.04, P = 0.01; odds ratio [OR]: 0.35, 95% CI: 0.18- 0.67, P = 0.002; OR: 0.45, 95% CI: 0.22-0.94, P = 0.03). There were no significant differences in the complication rates or Physiology and Chronic Health Evaluation II (APACHE II) scores in patients with or without corticosteroid therapy. **Conclusion:** Corticosteroid therapy may improve outcomes in patients with SAP.

KEYWORDS : Corticosteroid, severe acute pancreatitis, meta-analysis

1. INTRODUCTION

Acute pancreatitis (AP) is initiated by auto digestion, defined as the activation of proteolytic and lipolytic enzymes within acinar cells and/or pancreatic ducts, which leads to inflammation and destruction of the pancreatic tissue. AP is associated with a high mortality rate, and its incidence has been increasing in recent years. Standard therapy for AP includes bowel rest, pain control, intravenous fluids, and correction of electrolyte and metabolic abnormalities. Patients with more severe presentations are treated with early enteral nutrition and are closely monitored to maintain adequate organ perfusion.

Despite these therapeutic interventions, ap- proximately 20% of patients with severe acute pancreatitis (SAP) will progress to systemic inflammatory response syndrome (SIRS), complicated by shock, multiorgan failure, and even death, within the first 72 hours after admission [1, 2]. SIRS is a response to the widespread systemic effects of proinflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin (IL)-β, IL-6, and phospholipase A_2 (PLA_2).

These circulating cytokines play major roles in SAP progression to a systemic process by activating the vascular endothelium, increasing capillary permeability, and triggering the migration of leukocytes into tissues throughout the entire body [3, 4]. Inhibitors of these proinflammatory cytokines can be beneficial for reducing the severity of SAP.

Corticosteroids have shown beneficial effects in animal models of AP and SAP [5- 7], potentially due to their effects on inflammatory mediators, such as cytokines, endotoxins, and free radicals [8, 9]. Corticosteroids were initially reported to induce pancreatitis in susceptible patients [10]. However, in 1952, corticosteroids were usedsuccessfully as nonspecific anti- inflammatory agents to treat AP [11].

Following this report, additional studies showed that corticosteroids suppress the release of inflammatory cytokines in AP [12-14]. In 1997, Lazar and colleagues found that rats treated with hydro- cortisone showed diminished IL-6 levels [15].

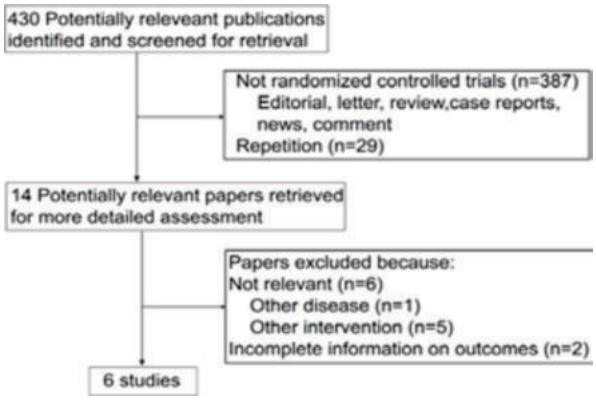


Figure 1. Six original RCTs were selected from 430 articles obtained from the electronic searches of MEDLINE, EMBASE, Web of Science, PubMed, Cochrane Library, Chinese Biomedicine Database, and China Academic Journal Full-Text Database. These RCTs were published from 2002 to 2010 and included 320 patients with SAP. We performed a meta- analysis to explore the potential effects of corticosteroids in patients with SAP.

2. METHODS

Search strategy

We performed a literature search in several electronic databases (i.e., MEDLINE, EMBASE, Web of Science, PubMed, Cochrane Library, Chinese Biomedicine Database, and China Academic Journals Full-Text Database), without any language restriction. The following search terms were used: "(acute pancreatitis OR severe acute pancreatitis) AND (steroid OR corticosteroid OR cortisol OR glucocorticoid OR dexametha SAP patients exhibit an influx of leukocytes into the pancreas [16]. Corticosteroids may relieve disease symptoms by inhibiting leukocyte activation [17]. Corticosteroids increase the activity of selected protease inhibitors [17, 18] and indirectly inhibit PLA_2 synthesis [19]. Administration of glucocorticoids attenuates pancreatic damage by protecting acinar cells [20]. When administered shortly before endotoxin, hydrocortisone greatly reduced the

clinical response to endotoxin in normal volunteers [21]. This interaction with endotoxin may represent another mechanism by which corticosteroids act.

Despite the positive results in animal models, the impact of corticosteroid therapy in patients with SAP remains unclear. Wan et al [22] found that corticosteroid therapy in SAP patients with SIRS decreased the risk of developing acute respiratory distress syndrome and shortened the length of hospitalization. Similarly, Xiang et al [23] reported that corticosteroid therapy ameliorated and abbreviated pathogenesis. However, most studies have not concluded whether corticosteroid therapy is useful in reducing rates ofcomplications, surgery, and mortality in SAP patients. Therefore, given the positive effects in animal experiments [24, 25], sone OR hydrocortisone OR prednisone OR prednisolone acetate OR methylprednisolone)" AND "("pancreatitis" [MeSH] AND "glucocorticoids" [MeSH])". References of selected studies were searched by hand.

A. Inclusion And Exclusion Criteria

Studies were included in the meta-analysis if they were randomized controlled trials (RCTs) enrolling participants, of any sex or ethnic origin, who had been diagnosed with SAP on the basis of clinical findings, elevated Creactive protein and serum amylase concentrations, and computed tomography (CT) results. SAP was defined by a history of typical abdominal pain associated with an increase in serum lipase values of at least twofold. SAP diagnosis was confirmed by CT. Severity was predicted by Ranson's score (≥ 3), Balthazar CT (≥ II), Acute Physiology and Chronic Health Evaluation II (APACHE II) scores (> 8), local complications (e.g., pancreatic necrosis, pseudocyst, and pancreatic abscess), or organ failure. Data on at least one of the following outcomes was required for inclusion: complication rates, changes in APACHE II scores, length of hospital stay, need for surgical intervention, or mortality.

Figure 2. Forest plots of the effects of corticoid treatment for patients with severe acute pancreatitis. Forest plots display values of the weighted mean difference (WMD), 95% confidence interval (CI), and odds ratio (OR). The diamond indicates the global estimate and its 95% CI.

B. Data Extraction And Methodological Quality

Two reviewers independently extracted the study data, including authors, publication year, study design, population, intervention, duration, and outcome. Disagreement was resolved by discussion. Methodological quality of the studies was scored by the Jadad scale, on the basis of the randomization method, allocation concealment, blinding of outcome assessment, and follow-ups. All included studies had a Jadad score of at least 2.

C. Statistical Analysis

Data were analyzed with Review Manager 5.0. Dichotomous data were presented as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical heterogeneity was measured using the chi-squared test and the inconsistency index (I^2). A *P*-value < 0.05 in the chi-squared test was considered to indicate statistically significant heterogeneity. The random- effects model was applied when obvious heterogeneity was present; otherwise, the fixed-effects model was used.

3. RESULTS

The literature search yielded 430 articles published from 1996 to 2013. After reviewing each publication, we selected six original RCTs that met the study criteria. These RCTs were published from 2002 to 2010 and included 320 SAP patients (Figure 1). Characteristics of each study are shown in Table 1. Allocation concealment was adequate in three studies. Blinding was not mentioned in any study. Follow-ups were completed in all studies. Baseline characteristics of patients included in each study were well matched between the treatment and control groups.

There was no significant difference in the complication rate between the experimental and control groups (OR: 0.65, 95% CI: 0.11 to 3.85, $P = 0.64$). Three RCTs [26-28] reported this outcome, with significant heterogeneity being observed among them ($I^2 = 83\%$, $P = 0.003$, Figure 2A). There was no significant difference in the APACHE II score changes between the two groups (weighted mean difference [WMD]: 1.07, 95% CI: -2.75 to 4.9, $P = 0.58$). Three RCTs [23, 28, 29] reported this outcome, with significant heterogeneity being observed among them ($I^2 = 96\%$, $P < 0.00001$, Figure 2B). Corticosteroid therapy had a significant effect on the length of hospital stay in patients with SAP (WMD: -9.47 95% CI: -16.91 to -2.04, $P = 0.01$). Six RCTs [22, 23, 26-29] reported this outcome, with significant heterogeneity being observed among them ($I^2 = 96\%$, $P < 0.00001$, Figure 2C). Significantly fewer patients in the experimental group required surgery compared to the control group (OR: 0.35, 95% CI: 0.18-0.67, $P = 0.002$). Included studies [22, 26-28] were homogeneous ($I^2 = 0\%$, $P = 0.40$, Figure 2D). Four RCTs [22, 26, 28, 29] assessed the effect of corticosteroid therapy on reducing the incidence of mortality.The mortality rate was significantly lower in the experimental group than in the con- trol group (OR 0.45, 95% CI: 0.22-0.94, $P = 0.03$). Homogeneity among the studies was observed ($I^2 = 0\%$, $P = 0.68$, Figure 2E)

4. DISCUSSION

In this meta-analysis of six RCTs, corticosteroid therapy reduced the length of hospitalization, the need for surgical intervention, and the mortality rate. Corticosteroid use not only lowered pain and hospitalization expenses, but also extended the survival of SAP patients. However, some researchers found an increased mortality rate after administering a high dose of hydro- cortisone treatment (100 mg/kg) [30]. Thus, we conclude that a relatively low dose (10 mg/kg) corticosteroids is helpful in the treatment of SAP.

Five of the six RCTs examined the effect of dexamethasone in the treatment of SAP, and one investigated the effect of methylprednisolone. The dexamethasone dosages differed in each study (range: 20-120 mg/day), and the duration of treatment ranged from 3 to 14 days. Wan et al. [22] studied the compound effect of dexamethasone and a Chinese herb decoction. Zhang et al. [28] studied the combined use of 6% hydroxyethyl starch, dexamethasone, and furosemide. Such combined interventions may have complicated the results, but the number of studies was limited. The diagnosis of SAP was based on similar, but not identical, criteria. Studies diagnosed SAP according to the "Atlanta" criteria [31], the National Conference for Pancreatic Diagnosis Standards [32], and the Guide to Diagnosis and Treatment of Acute Pancreatitis in China [33]. Although all of the studies were prospective and randomized, none was blinded. Therefore, the possibility of investigator bias must be considered.

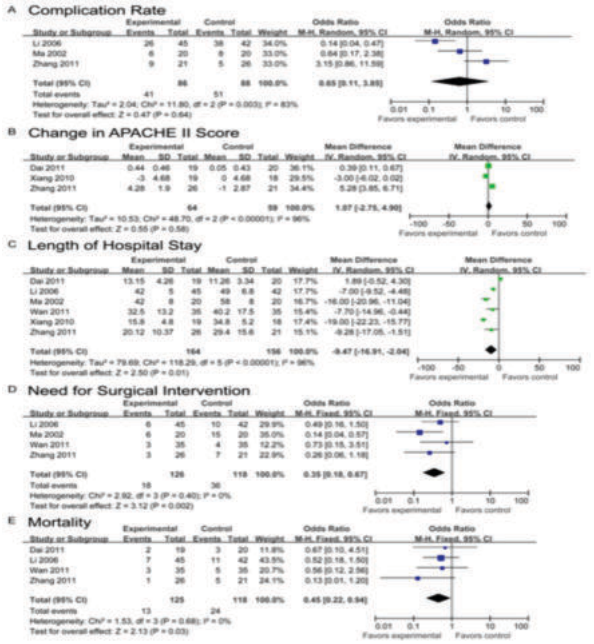
In conclusion, corticosteroid therapy can benefit SAP patients by reducing the length of hospital stay, the need for surgical intervention and the mortality rate. Future well-designed RCTs of adequate size and duration are needed to explore the effects of corticosteroids in SAP patients.

5. Table

Table 1. Methodological characteristics of studies included in this meta-analysis

Study	Sample size	Randomization	Blinding	Intervention	Confounding factor	Duration	Follow-up
Wan et al. [22] (China 2011)	70 (35/35)	Table of numbers	No	1mg/(kg * day) dexamethasone	Modified Dachengqi decoction	3 days	Yes

Xiang et al. [23] (China 2010)	37 (19/18)	Yes	No	10 mg* (2-3)/day dexamethasone	None	3-5 days	Yes
Li et al. [26] (China 2006)	87 (45/42)	Yes	No	20-30 mg* (2-3)/day dexamethasone and 16- 20 mg/day composite salvia miltiorrhiza	Composite salvia miltiorrhiza	3-5 days	Yes
Ma et al. [27] (China 2002)	40 (20/20)	Table of numbers	No	80-100 mg/day dexamethasone	None	14 days	Yes
Zhang et al. [28] (China 2011)	47 (26/21)	Yes	No	10 mg* 3/day dexamethasone combined with 6% hydroxyethyl starch 130/0.4 and furosemide	combined use of 6% hydroxyethyl starch 130/0.4 and furosemide	7 days	Yes
Dai et al. [29] (China 2011)	39 (19/20)	Table of numbers	No	1 mg/(kg* day) methylprednisolone	None	5 days	Yes



6. Figures

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