Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease (Review)

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[Intervention Review]

Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease

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ABSTRACT

Background

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are a major cause of hospital admission and mortality. They contribute to long-term decline in lung function, physical capacity and quality of life. The most common causes are infective, and treatment includes antibiotics, bronchodilators and systemic corticosteroids as anti-inflammatory agents.

Objectives

To assess the effects of corticosteroids administered orally or parenterally for treatment of acute exacerbations of COPD, and to compare the efficacy of parenteral versus oral administration.

Search methods

We carried out searches using the Cochrane Airways Group Specialised Register of Trials, MEDLINE and CENTRAL (Cochrane Central Register of Controlled Trials), and checked references of included studies and trials registries. We conducted the last search in May 2014.

Selection criteria

Randomised controlled trials comparing corticosteroids administered orally or parenterally with an appropriate placebo, or comparing oral corticosteroids with parenteral corticosteroids in the treatment of people with acute exacerbations of COPD. Other interventions (e.g. bronchodilators and antibiotics) were standardised for both groups. We excluded clinical studies of acute asthma.

Data collection and analysis

We used standard methodological procedures expected by The Cochrane Collaboration.

Main results

Sixteen studies (n = 1787) met inclusion criteria for the comparison systemic corticosteroid versus placebo and 13 studies contributed data (n = 1620). Four studies (n = 298) met inclusion criteria for the comparison oral corticosteroid versus parenteral corticosteroid and three studies contributed data (n = 239). The mean age of participants with COPD was 68 years, median proportion of males 82% and mean forced expiratory volume in one second (FEV_1) per cent predicted at study admission was 40% (6 studies; n = 633). We judged risk of selection, detection, attrition and reporting bias as low or unclear in all studies. We judged risk of performance bias high in one study comparing systemic corticosteroid with control and in two studies comparing intravenous corticosteroid versus oral corticosteroid.

Systemic corticosteroids reduced the risk of treatment failure by over half compared with placebo in nine studies (n = 917) with median treatment duration 14 days, odds ratio (OR) 0.48 (95% confidence interval (CI) 0.35 to 0.67). The evidence was graded as high quality and it would have been necessary to treat nine people (95% CI 7 to 14) with systemic corticosteroids to avoid one treatment failure. There was moderate-quality evidence for a lower rate of relapse by one month for treatment with systemic corticosteroid in two studies (n = 415) (hazard ratio (HR) 0.78; 95% CI 0.63 to 0.97). Mortality up to 30 days was not reduced by treatment with systemic corticosteroid compared with control in 12 studies (n = 1319; OR 1.00; 95% CI 0.60 to 1.66).

FEV_1, measured up to 72 hours, showed significant treatment benefits (7 studies; n = 649; mean difference (MD) 140 mL; 95% CI 90 to 200); however, this benefit was not observed at later time points. The likelihood of adverse events increased with corticosteroid treatment (OR 2.33; 95% CI 1.59 to 3.43). Overall, one extra adverse effect occurred for every six people treated (95% CI 4 to 10). The risk of hyperglycaemia was significantly increased (OR 2.79; 95% CI 1.86 to 4.19). For general inpatient treatment, duration of hospitalisation was significantly shorter with corticosteroid treatment (MD -1.22 days; 95% CI -2.26 to -0.18), with no difference in length of stay the intensive care unit (ICU) setting.

Comparison of parenteral versus oral treatment showed no significant difference in the primary outcomes of treatment failure, relapse or mortality or for any secondary outcomes. There was a significantly increased rate of hyperglycaemia in one study (OR 4.89; 95% CI 1.20 to 19.94).

Authors' conclusions

There is high-quality evidence to support treatment of exacerbations of COPD with systemic corticosteroid by the oral or parenteral route in reducing the likelihood of treatment failure and relapse by one month, shortening length of stay in hospital inpatients not requiring assisted ventilation in ICU and giving earlier improvement in lung function and symptoms. There is no evidence of benefit for parenteral treatment compared with oral treatment with corticosteroid on treatment failure, relapse or mortality. There is an increase in adverse drug effects with corticosteroid treatment, which is greater with parenteral administration compared with oral treatment.

PLAIN LANGUAGE SUMMARY

Do systemic corticosteroids improve treatment outcomes in flare-ups of chronic obstructive pulmonary disease?

Why is this question important?

Chronic obstructive pulmonary disease (COPD), also referred to as emphysema or chronic bronchitis, is a long-term lung condition commonly associated with smoking. People with COPD usually have persistent symptoms of breathlessness and may experience flare-ups (exacerbations) on occasion, often precipitated by infection, in which symptoms become markedly worse and further medical intervention is required beyond regular treatment by inhalers.

Systemic (i.e. not inhaled corticosteroids) such as prednisolone, prednisone and cortisone, are anti-inflammatory drugs commonly used in the treatment of exacerbations. We wanted to assess the effectiveness of systemic corticosteroids and whether different routes of administration have impacts on response to treatment of COPD exacerbations.

How did we answer the question?

We looked for all studies that compared corticosteroid, given either by injections (parenterally) or tablets (orally), with matching dummy injections or tablets and all studies that compared corticosteroid given by injections with corticosteroid given by tablets.

What did we find?

We found 16 studies including over 1700 people with COPD who experienced a flare-up that required additional medical treatment that compared corticosteroid given by injections or tablets with dummy treatment. Four studies with nearly 300 people compared corticosteroid injections with corticosteroid tablets. More men than women took part in the studies and they were usually in their late 60s, with moderately severe symptoms of COPD. Most studies took place in hospitals, two in intensive care units with people who needed breathing support, and three studies involved people who were treated at home. The last search for studies to include in the review was done in May 2014.

There were three studies where people knew which treatment they were getting, but otherwise studies were generally well designed.

People treated with either corticosteroid injections or tablets compared with dummy treatment were less likely to experience treatment failure, 122 fewer people per 1000 treated, with a lower rate of relapse by one month. They had shorter stays in hospital if they did not require assisted ventilation in an intensive care unit, and their lung function and breathlessness improved more quickly during treatment. However, they had more adverse events while taking treatment, especially a temporary increase in glucose levels in blood. Corticosteroid treatment did not reduce the number of people who died within one month of their flare-up.

In studies comparing two ways of giving corticosteroid, either by injections or tablets, there were no differences in treatment failure, the time in hospital or number of deaths after discharge; however, a temporary increase in glucose levels in blood was more likely with injections than tablets.

Conclusion

There is high-quality evidence that is unlikely to be changed by future research that people who experience flare-ups of COPD benefit from treatment with corticosteroid given by injections or tablets with the increased risk of some temporary side effects.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Systemic corticosteroid compared with placebo for acute exacerbations of COPD

Patient or population: acute exacerbations COPD
Settings: outpatient, inpatient and people in ICU
Intervention: systemic corticosteroid
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
		Systemic corticosteroid				
Treatment failure Need to intensify therapy/ ED or hospital admission Follow-up: 3-30 days	**276 per 1000**	**154 per 1000** (118 to 203)	**OR 0.48** (0.35 to 0.67)	917 (9 studies)	⊕⊕⊕⊕ **high**	-
Relapse Treatment for AE of COPD or hospital re-admission Follow-up: 1-4 months	**215 per 1000**	**174 per 1000** (122 to 242)	**OR 0.77** (0.51 to 1.17)	596 (5 studies)	⊕⊕⊕◯ **moderate**[1]	In 2 studies (n = 415) relapse to 1 month was lower with systemic corticosteroid compared with placebo (HR 0.78; 95% CI 0.63 to 0.97
Improvement in lung function - early effect FEV_1 (L) as absolute or change Follow-up: 3 days	The mean FEV_1 in control groups ranged from 0.77 to 0.91 L	The mean early improvement in lung function in the intervention group was **0.14 L higher** (0.09 to 0.20 higher)	-	649 (7 studies)	⊕⊕⊕⊕ **high**	-

Decreased breathlessness - early effect Borg scale or VAS Follow-up: 3 days	The mean change in breathlessness in control group was 1.8 units using the Borg scale and 1.5 units on the VAS scale	The mean early decrease in breathlessness in the intervention group was **0.35 standard deviations higher** (0.05 to 0.64 higher)	-	178 (3 studies)	⊕⊕⊕○ **moderate**[2]	Effect size on Borg scale 0.93 units; 95% CI 0.18 to 1.7 (MCID = 2); effect size on VAS scale 5.24; 95% CI 0.75 to 9.59 (MCID = 10)
Adverse drug effect Follow-up: 2-26 weeks	**285 per 1000**	**481 per 1000** (388 to 577)	**OR 2.33** (1.59 to 3.43)	736 (8 studies)	⊕⊕⊕⊕ **high**	-
Hyperglycaemia	**124 per 1000**	**282 per 1000** (208 to 371)	**OR 2.79** (1.86 to 4.19)	804 (6 studies)	⊕⊕⊕⊕ **high**	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
AE: acute exacerbation; **CI:** confidence interval; **COPD:** chronic obstructive pulmonary disease; **ED:** emergency department; **FEV_1:** forced expiratory volume in 1 second; **HR:** hazard ratio; **MCID:** minimum clinically important difference; **OR:** odds ratio; **VAS:** visual analogue scale.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Wide CIs include significant benefit and harm (-1 for imprecision).
[2] Upper or lower CI of effect size crosses 0.5 (-1 for imprecision).