Clinical, cellular and molecular effects of topical and systemic corticosteroids on the inflammatory response to intradermal lipopolysaccharide administration in healthy volunteers

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Background

Intradermal LPS challenge in healthy volunteers has proven to be a valuable tool to study local inflammation *in vivo*. In the current study corticosteroids (topical clobetasol and oral prednisolone) were selected to quantify their inhibitory effect on intradermal LPS challenge and as benchmark for other presumed inhibitors.

Objective

To quantify the anti-inflammatory effect of clobetasol and prednisolone on the intradermal LPS challenge in healthy volunteers.

Methods

24 healthy male volunteers received a 2.5 day pre-treatment with topical clobetasol propionate 0.05% and six healthy volunteers received a 2.5 day pre-treatment with oral prednisolone at 0.25 mg/kg bodyweight per administration, prior to LPS administration. Subjects received either 0, 2 or 4 intradermal LPS injections (10ng LPS in 100µL 0.9% NaCL solution). The LPS response was evaluated by non-invasive (perfusion, skin temperature, and erythema) and invasive assessments (cellular and cytokine responses) in suction blister exudate.

Results

Both corticosteroids were able to significantly suppress the clinical inflammatory response (erythema, heat, perfusion). Topical clobetasol also significantly reduced the number of inflammatory cells quantified in the blister exudate, a similar trend was observed for prednisolone pre-treated subjects. No relevant changes were observed in the cytokine response to LPS after pre-treatment with corticosteroids.

Conclusions

We have successfully demonstrated that the immunosuppressive effects of corticosteroids can be detected using our intradermal LPS challenge model, validating the model for evaluation of future investigational drugs targeting TLR4-mediated signaling pathways.

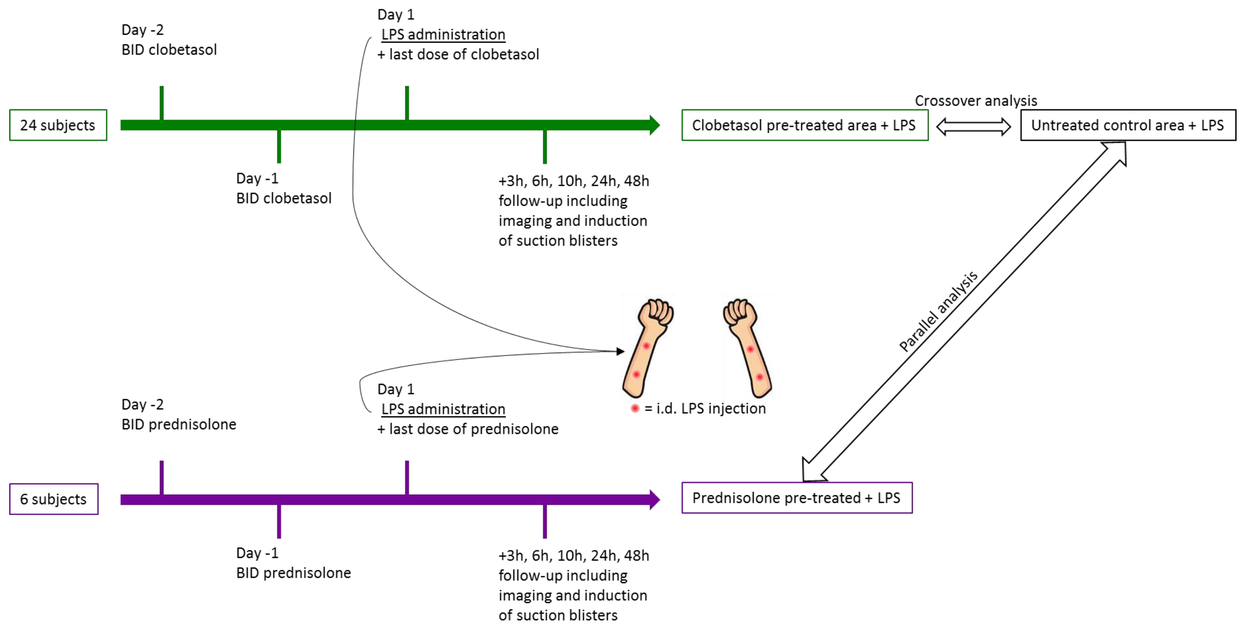

Figure 1. Graphical display of the study design. Subjects were pre-treated with either topical clobetasol or oral prednisolone at body weight 2.5 days prior to LPS administration. Follow-up took place 3h, 6h, 10h, 24h, and 48h after LPS administration.

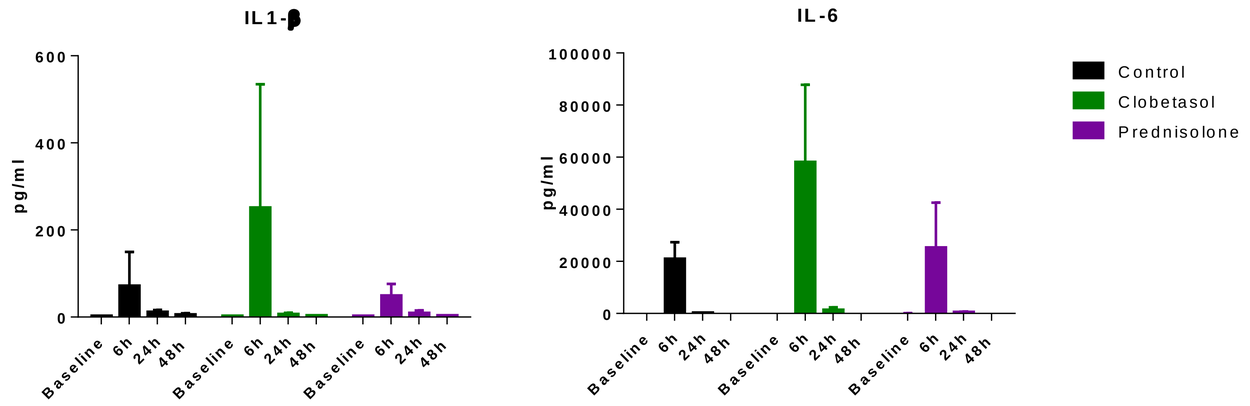

Figure 2. Topical and systemic corticosteroids do not affect the LPS-driven cytokine responses. Cytokine concentrations in blister exudate were analysed by MSD. Data are presented as mean ± SD.

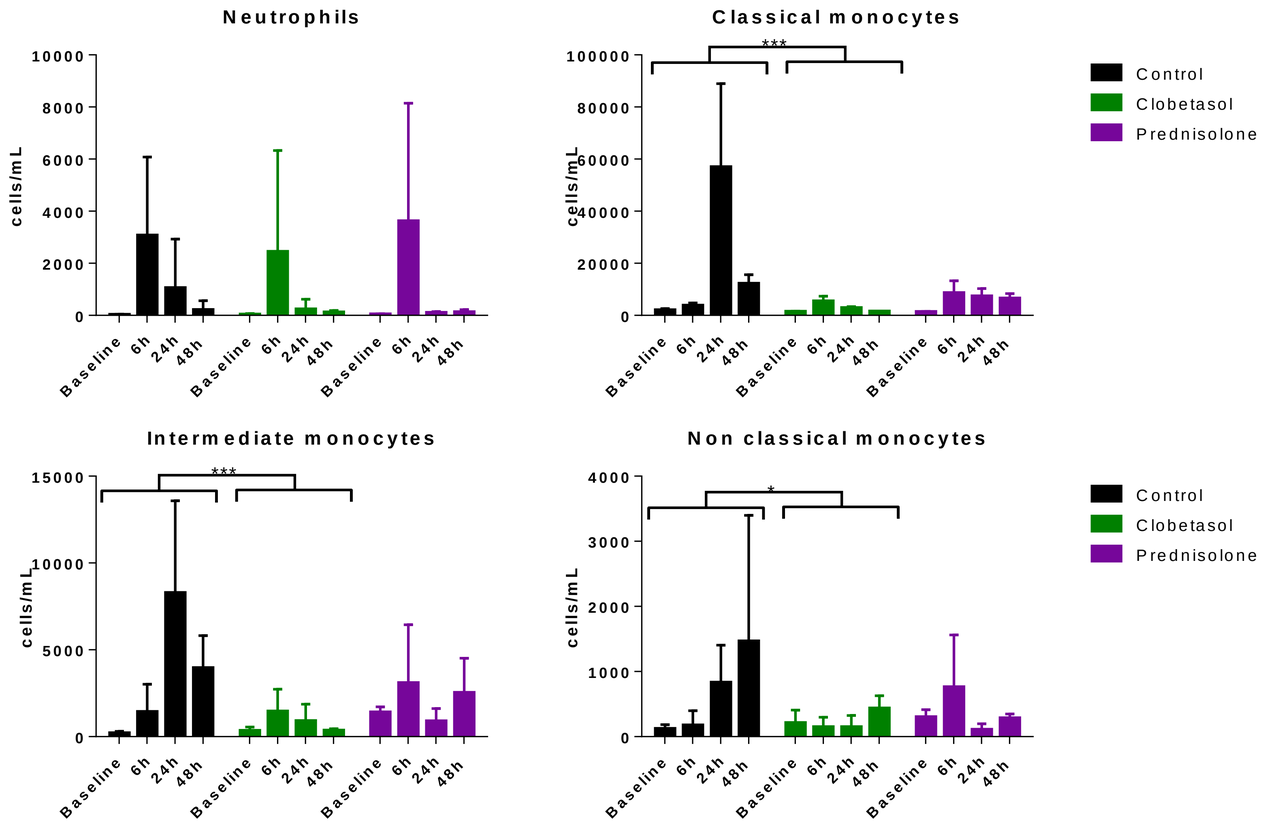

Figure 3. Topical and systemic corticosteroids reduced the LPS-driven immune cell infiltration except for neutrophils. Immune cells were quantified in blister exudate by flow cytometry at different time points after LPS administration. Data are presented as mean ± SEM. * P < 0.05 and *** P < 0.0001. Prednisolone showed a comparable anti-inflammatory effect, although not statistically significant, likely because of a lack of power due to the parallel analysis and fewer subjects than clobetasol versus control.

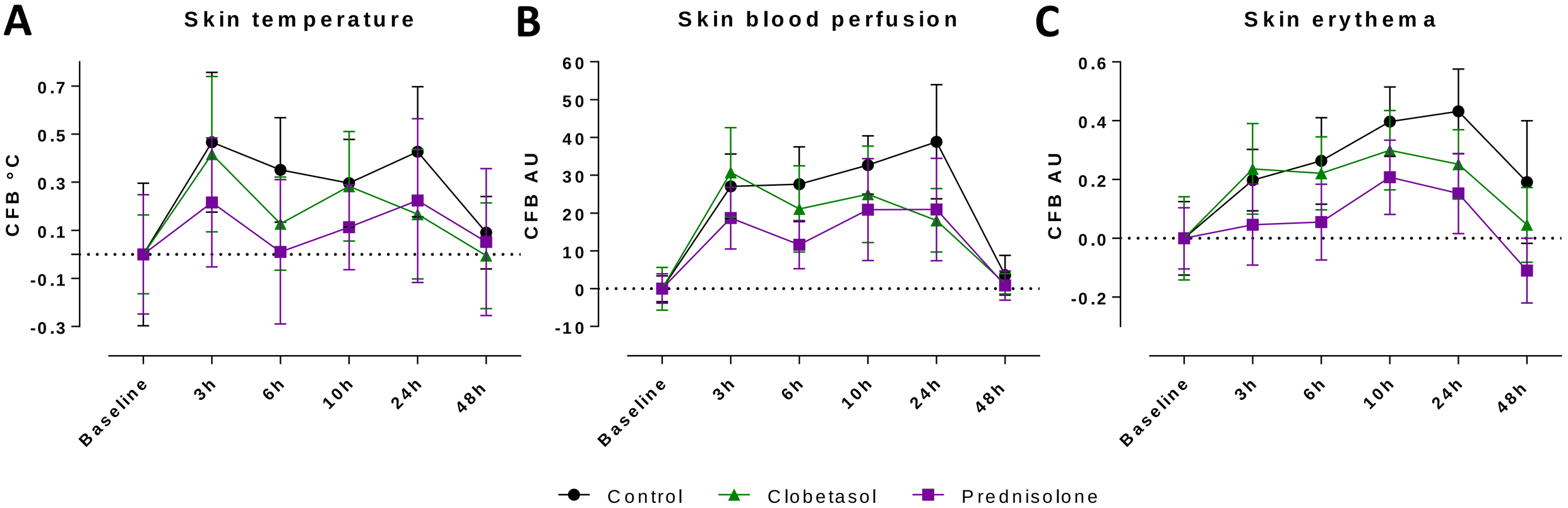

Figure 4. Topical clobetasol or oral prednisolone successfully reduced the inflammatory response to intradermal LPS. The inflammatory response was analysed by quantifying temperature (3A), skin blood perfusion (3B) and skin erythema (3C). All data are presented as mean ± SD. Because the induction of a suction blister disqualified the area for further follow-up, the sample size decreased over time. The sample size was as follows: baseline 24 measurements, 3h 18 measurements, 6h 18 measurements, 10h 12 measurements, 24h 12 measurements and 48h 6 measurements.