Steroids pulse-therapy for Covid-19 and SARS / G. Dolci et al.

Supplementary file

Review protocol
The review protocol was registered on the PROSPERO database with ID CRD42020190183 (1).

Literature search and study selection
A systematic literature review was conducted on May 14th and again on November 7th 2020, ending on the same days, independently by two authors (GD and GC) using 5 databases: PubMed, Web of Science, Scopus, Latin American and Caribbean health Sciences Literature (LILACS) and Cochrane Central. The research strategies were ((glucocorticoid* OR corticosteroid* OR steroid*) AND (SARS* OR MERS* OR COVID*) AND (puls* OR bol*)) in word, title and abstract sections; where possible they were also searched in all fields and “registro de ensayos clinicos” sections. Detailed research strategies and results are described in Table S1. References from review articles and meta-analyses focusing on SARS-CoV, MERS-CoV and SARS-CoV2 were examined to identify additional studies. Duplicated studies were first excluded, and then titles and abstracts were carefully scanned by two authors (GD and GC). Studies were included if they met all of the following criteria (Table S2): 1) Patients with SARS-CoV, MERS-CoV or SARS-CoV2 infection; 2) Treatment with methylprednisolone 500mg/day or more or other corticosteroids equivalent doses; 3) Any study design. If the dose of steroids was not determinable from title nor abstract, articles were not excluded and they were then evaluated using the full text. After the evaluation of the full text, reviews were excluded and relevant cited papers checked for eligibility. If full text was not available, the publishing Journal or the authors were contacted by email or if available through ResearchGate to request a copy. If data from full text were not clear, authors were contacted by email or if available through ResearchGate to ask for further details.

For the primary outcomes concerning treatment efficacy, only studies that directly compared pulse-therapy and any other treatment were considered. For the secondary outcomes, concerning treatment safety (apart from oro-tracheal intubation), both comparative and non-comparative studies were included. If the number of patients receiving pulse-therapy was not available, the study was excluded.

No language restriction was considered. One full-text in Chinese was available after contacting authors and journals and it did not meet the criteria for inclusion in the primary outcome analysis. One full-text in Russian was available (2): it was evaluated and data were extracted by only one author J.M. No years of publication restriction was applied and only published articles were considered. This study was done in accordance with PRISMA recommendations.

Data extraction and management
Data regarding the papers were managed using Mendeley (Elsevier®). Data for every included study were collected in an Excel (Microsoft®) sheet including all main article characteristics and study outcomes.

Statistical analysis
We synthesised results in tables for primary outcomes and secondary outcomes, divided for disease (one for SARS, one for MERS and one for MERS-CoV or SARS-CoV2 infection). For the primary outcomes and secondary outcomes, statistical analysis was conducted using Mendeley (Elsevier®). Data for every included study were collected in an Excel (Microsoft®) sheet including all main article characteristics and study outcomes.

Table S1. Research strategies and research results.

<table>
<thead>
<tr>
<th>Database</th>
<th>Research strategy</th>
<th>Papers found</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed</td>
<td>(((glucocorticoid* OR steroid* OR corticosteroid*)) AND (puls* OR “high dose”)) AND (COVID19 OR COVID-19 OR SARS-CoV2 OR SARS OR MERS OR Coronavirus)</td>
<td>115</td>
</tr>
<tr>
<td>Web of Science</td>
<td>TOPIC: (glucocorticoid* OR corticosteroid* OR steroid*) AND TOPIC: (COVID* OR SARS-CoV2 OR MERS* OR Coronavirus*) AND TOPIC: (puls* OR high dose)</td>
<td>128</td>
</tr>
<tr>
<td>Scopus</td>
<td>(TITLE-ABS-KEY (glucocorticoid* OR steroid*) OR corticosteroid*) AND TITLE-ABS-KEY (puls* OR bol*) AND TITLE-ABS-KEY (sars* OR covid* OR mers* )</td>
<td>88</td>
</tr>
<tr>
<td>LILACS</td>
<td>glucocorticoid* OR steroid* OR corticosteroid* [Titulo, resumen, asunto] and COVID* OR SARS* OR MERS* [Titulo, resumen, asunto] and puls* OR bol* [Titulo, resumen, asunto]</td>
<td>70</td>
</tr>
<tr>
<td>Cochrane Central</td>
<td>glucocorticoid* OR corticosteroid* OR steroid* in Title Abstract AND COVID* OR SARS* OR MERS* OR Coronavirus* in Title Abstract Keyword AND puls* OR bol* in Title Abstract Keyword - (Word variations have been searched)</td>
<td>23</td>
</tr>
</tbody>
</table>

Table S2. Systematic literature review’s P.I.C.O.S.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Patients with SARS, MERS or SARS-CoV2 infection</td>
<td>Treatment defined as “pulse therapy” but &lt;500mg/day of Methylprednisolone or equivalent</td>
</tr>
<tr>
<td>Intervention</td>
<td>Methylprednisolone 500mg/day or more or equivalent dose of other glucocorticoids</td>
<td></td>
</tr>
<tr>
<td>Comparator</td>
<td>Any other treatment</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>Death, ICU admission, intubation</td>
<td></td>
</tr>
<tr>
<td>Study design</td>
<td>Randomised and non-randomised controlled trial, single arm trial, prospective and retrospective cohort studies, case series</td>
<td>Reviews</td>
</tr>
</tbody>
</table>

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Supplementary file

Clinical and Experimental Rheumatology 2021
COVID19). We decided not to perform quantitative synthesis due to the low quality of included comparative studies focusing on steroids pulse therapy compared to other therapies.

Data synthesis
We directly extracted the total number of deaths and ICU admission from the included papers. This was a discrepancy from the study protocol and it has been done because of the inclusion of only six studies in the primary endpoints analysis, with high risk of bias and heterogeneity.

Results
Twenty-two papers describing patients that received glucocorticoids pulse-therapy in COVID-19 were found, but eleven were excluded because the number of patients that received pulse-therapy was not available or the pulse-therapy dose was lower than 500mg/day of methylprednisolone. No paper was found for MERS, while 32 papers regarding SARS, 21 describ-
ing the acute phase of the disease and 11 describing the sequelae of the considered patients (Table S3a and Table S3b). The number of patients that received pulse-steroids therapy was reported in 18 out of 32 papers and these 18 were included in the systematic review. Of these 18 papers, 10 reported the number of patients died and 6 the number of patients admitted to ICU among the ones that received pulse-therapy.

Two papers directly focusing on pulse-therapy compared to non-pulse therapies were found (3, 4) for SARS and four were found for COVID-19 and they were considered for efficacy outcomes (Table S1) and assessed for risk of bias.

The secondary outcomes of this systematic review were available as follow: 5 for oro-tracheal intubation; 0 for osteonecrosis; 2 for hyperglycaemia; 0 for psychosis; 2 for super-infections (Table S3b).

Risk of bias assessment
The quality of the evidence was very low for both outcomes and both included studies had an high overall risk of bias using ROBINS-I tool (5) (Table S4).

References

Table S4. Risk of bias evaluation using ROBINS-I tool for the two papers on SARS and the four papers on COVID-19 included in the primary outcomes analysis.


