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Corticosteroids therapy in pediatric acute respiratory distress syndrome

Uso de corticosteroide na síndrome do desconforto respiratório agudo em pacientes pediátricos

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ABSTRACT

The use of corticosteroids in acute lung injury and acute respiratory distress syndrome is one of the most controversial issues in the literature. However, acute lung injury/acute respiratory distress syndrome studies are restricted to adults, despite the widespread use of corticosteroid for hyper-reactive respiratory airway diseases in children. This review aimed to describe experimental and clinical evidence for corticosteroid therapy in acute lung injury/acute respiratory distress syndrome and to point out the risks and benefits of its use in pediatrics. For this purpose, an extensive review of the literature was performed from 1980 to 2010 including both experimental and clinical papers, as well as reviews and meta-analysis, using Medline, Cochrane Central Register of Controlled Trials, Cochrane database of systematic reviews, SciELO, Lilacs and Bireme databases. The search terms were: acute lung injury, acute respiratory distress syndrome, steroids, child, clinical trials, meta-analyses, reviews, and case reports. Most studies showed that the corticosteroids-induced down-regulation of systemic inflammatory response is associated with oxygenation improvement, reduction of multiple organ dysfunctions, mechanical ventilation time, and intensive care units length of stay. Based on the literature, the authors suggest early and prolonged methylprednisolone administration for acute lung injury/acute respiratory distress syndrome, using continuous 1 mg/kg/day infusion to prevent glycemic variability, associated with strict infection surveillance. In addition, they recommend some diagnostic parameters, interventions and choices of endpoint variables to be adjusted to improve pediatric trials feasibility. Therefore, more research is required to establish the safety and efficacy of methylprednisolone in pediatric patients with acute lung injury/acute respiratory distress syndrome , as well as to determine the best parameters for monitoring steroid side effects and outcomes.

Keywords: Acute lung injury; Respiratory distress syndrome adult; Adrenal cortex hormones; Child; Clinical trials; Meta-analysis

INTRODUCTION

Since the pathophysiology of acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) involves intensive inflammatory lung reaction, for the last three decades, researchers have been involved in demonstrating the benefits of corticosteroid, a widely available and low-cost drug.[1-15] In spite of evidence that corticosteroids improve lung and other organs functions in

adults with ARDS,[5,6,8-15] its effectiveness in reducing mortality (35.8% in adults and 18% in children)[16] is still controversial among several randomized clinical trials and meta-analysis.[7,9,12-14,17-21] Although corticosteroids are widely used in bronchial hyperreactivity-associated respiratory diseases in children, studies on their use in pediatric ALI/ARDS are limited to some case reports. ARDS is frequently underdiagnosed in children shaded by other most frequent underlying diagnosis (bronchiolitis, sepsis and pneumonia). In addition, its lower incidence, shorter mechanical ventilation time and lower mortality rate are challenging for the conduction of pediatric trials. Larger samples and other endpoints than mortality are required in order to allow statistical relevance.[22]

This article involved a review of ALI/ARDS pathophysiology and mechanism of action of corticosteroids, and discussed the most relevant clinical and experimental studies and meta-analysis on the early use of prolonged infusion of low-dose corticosteroids in ALI/ARDS, as well as its adverse effects. Based on the data discussed, some diagnosis, intervention and endpoints selection adjustments are proposed to improve pediatric trials feasibility.

ALI/ARDS pathophysiology

ALI/ARDS is characterized by intense pulmonary inflammatory reaction, acutely developing in 12 to 48 hours in the context of a severe systemic illness resulting in hypoxemic respiratory failure. The typical lung histological finding in ARDS is diffused alveolar damage, which involve the alveolar-capillary membrane, associated with increased permeability, protein rich neutrophilic exudate, interstitial and alveolar edema, and hyaline membranes, leading to worsened gas exchange and reduced pulmonary compliance.[21]

There is a strong correlation between persistent pulmonary and systemic inflammation and mortality after the first week of ALI/ARDS.[5,23,24] The inability to down regulate inflammatory mediators production is related to an inappropriate alveolar-capillary membrane repair and impaired pulmonary gas exchange and compliance.[5,25,26]

Mechanism of action of corticosteroids

Corticosteroids have potent anti-inflammatory actions, including the reduction in number and function of several immune cells, such as T and B type lymphocytes, monocytes, neutrophils, eosinophils at sites of inflammation. Corticosteroids decrease the production of cytokines and eicosanoids, and increase the production of macrophage migration inhibitory factor. After captured from the circulation, corticosteroids bind to intra-cellular glucocorticoids receptors (GRs) in the cytoplasm, resulting in the activation of glucocorticoid-receptor (GC-GR) complex. The GC-GR complex then moves into the nucleus and promotes activation or repression of the transcription of associated genes.[25,27] It has been estimated that corticosteroids affect twenty per cent of the genome of mononuclear blood cells.[27] The GC-GR complex may also indirectly affect cell function by binding to and modulating transcription factors such as NF (nuclear factor)- κB.[28]

The latent NF-κB, usually bound to inhibitory proteins in the cytoplasm (I-κB), is activated by several stimuli, such as lipopolisaccharide, physical or chemical stress, and inflammatory cytokines. This activation induces translocation of NF-κB into the nucleus where it binds to promoter regions of target genes to initiate the transcription of multiple cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1 and IL-6, intracellular adhesion molecule 1, selectin E, and other inflammatory mediators. Corticosteroids may inhibit NF-κB activity either by directly binding to it or increasing I-κB proteins transcription.[29]

Mediators released in severely ill patients, particularly those with sepsis, may either stimulate or impair synthesis and action of cortisol by direct action on the hypothalamic-pituitary-adrenal axis and glucocorticoid receptors. Clinical and experimental data suggest that refractory sepsis and ARDS are frequently associated with a condition known as critical illness-related corticosteroid insufficiency (CIRCI).[30,31] This condition is characterized by a failure of activated GRs to down-regulate the transcription of inflammatory cytokines, in spite of high cortisol circulating levels. These findings provide biochemical and molecular base evidence to support the pharmacological efficacy of methylprednisolone in ARDS. Longitudinal analysis of biomarkers provided evidence that prolonged methylprednisolone therapy modified CIRCI, increased GC-GRα complex activity and reduced NF-κB binding. Consequently, reduction in plasma and bronchoalveolar lavage (BAL) levels of pro-inflammatory mediators, chemokines, adhesion molecules and fibrinogenic markers were observed, as well as increase in anti-inflammatory cytokines (IL-10) levels, with improvement in alveolar-capillary membrane permeability.[15,21,25,27]

Experimental trials

Experimental studies regarding the use of corticosteroids in ALI/ARDS have controversial results, which may

be ascribed to differences related to animal models, injury magnitude, drug type and mode of administration.

Time of the drug introduction

The use of corticosteroids 6 hours after paraquat-induced ALI reduced pulmonary fibrosis.[32] In mice, the injection of dexamethasone 12 hours before lipopolysaccharide (LPS) blocked TNF production. However its use 24 to 48 hours before LPS administration lead to TNF increase by means of poorly understood mechanisms.[33] Similar results were found in healthy volunteers treated with corticosteroid concomitantly to LPS insult. There was a reduction of temperature and pulse response, suppression of epinephrine and C reactive protein peak, and inhibition of TNF production. However, circulating TNF and IL-6 increased when corticosteroid was given 12 or 144 hours before the insult.[34] These results suggest that hypercortisolemia previous to the infectious insult was a determinant factor for hemodynamic, hormonal and inflammatory regulation, and raised the issue that the use of prophylactic corticosteroids could be detrimental in ADRS.

Treatment dose and duration, and tapering

An *in vitro* study evaluated alveolar macrophage responses to different doses and duration of therapy with dexamethasone after LPS exposure in different animal models. It was concluded that short term high doses or prolonged term low doses increased the production of inflammatory mediators (IL-1β and nitric oxide), while prolonged high doses reduced inflammatory response.[35] Conversely, Silva et al. have shown that short term was equally effective as long term therapy, when low methylprednisolone (2 mg/kg) doses were used during early LPS-induced ALI.[36]

The rebound effect after early corticosteroid therapy discontinuation as well as the influence of dose and therapy duration were shown in butylated-hydroxytoluene induced ALI. Methylprednisolone administration in the first 5 or 6 days lead to enhanced accumulation of lung tissue collagen,.while maintaining therapy for 12 days prevented fibrogenesis. A rebound effect was seen upon discontinuation.[37,38] High dose prednisolone or methylprednisolone (30 mg/kg, bid) given later (3rd to 7th day or 6th to 10th day) or for longer periods (1st to 10th day), or in lower doses, did not mitigate fibrosis development.[37,38]

ALI/ARDS etiology

The intensity of corticosteroid anti-inflammatory and anti-fibrinogenic activity was different according to ALI etiology (either pulmonary or extra-pulmonary). The beneficial effect was more intense in pulmonary ALI compared to extra-pulmonary ALI.[39] These controversial results suggest how limited is our knowledge on this subject, and also the existence of a complex temporal relationship between corticosteroid induced hypercortisolemia and induced inflammatory response by pulmonary insult.

Clinical trials

Controversies were also identified in clinical trials, wich may be partially explained by the great heterogeneity between corticosteroid treatment schedules. Short treatment duration, rather than drug dose or time of introduction is believed to be responsible for masking the beneficial effects of corticosteroids in the large randomized trials evaluating high doses of methylprednisolone during ARDS exudative and fibrin proliferative phases. Based on experimental studies, recent clinical trials have used early corticosteroid administration in the first 72 hours, at lower doses, for longer periods (at least ≥ 7 days) and tapering withdrawal, conditions considered to be relevant for drug effectiveness.[15]

Twelve clinical trials investigating prolonged-low dose corticosteroid therapy initiated either early (first 72 hours) or late (≥ 7 days) in the course of ALI/ARDS were selected. Studies using other than these therapeutic schedules (short term, high doses) were not included. Table 1 displays trials related to late corticosteroid therapy. In this context, low to moderate methylprednisolone doses (1 to 3.5 mg/kg/day) were given for prolonged time ranging from 7 to 32 days.[1,5-10,14] The time of corticosteroid introduction was also variable, ranging from 6 to 44 days. Only two trials[9,14] have showed no ALI/ARDS mortality reduction. A large, multi-center randomized trial conducted by ARDS network[14] found no difference in 60 and 180 days mortality rate as compared to placebo. However, when subgroups 1 (less than 14 days of illness) and 2 (14 or more days of illness) were separately analyzed, mortality rate was higher for subgroup 2 compared to placebo. Nevertheless, in this subgroup (n=48) there was a wide variability in baseline characteristics. After adjusting for this variability, the mortality difference lost statistical significance. The introduction of methylprednisolone after two weeks of ARDS increases mortality risk.[19] Beneficial effects of corticosteroids were seen during the first part of this trial, such as: 10 day reduction of mechanical ventilation duration, two fold increase in the success rate of extubation, and a 27% reduction in the relative risk of mortal-

Table 1 – Low-dose corticosteroid in late ALI/ARDS

Author	Ashbaugh[1] 1985	Biffl[6] 1995	Meduri[5] 1994	Keel[7] 1995/1998	Varpula[9] 1998/2000	Huh[10] 1998/2002	Meduri[8] 1998	Steinberg[14] 2006
Study design	Case series	Case series	Case series	Retrospective cohort	Retrospective cohort	Retrospective cohort	Multi-center RCT (4 centers)	Multi-center RCT (25 centers)
Patients numbers	10	6	25	31	31	48	24	180
MP/Dose	125mg/dose EV-6/6h	1-2 mg/kg/ dose EV-6/6h	200mg bolus + 2-3 mg/kg/ day 6/6h until extubation	100-250 mg/ day for 3 days; then 80-180 mg	120 mg/day for 3 days	140 mg/kg/ day	2mg/kg bolus + 2 mg/kg/day 6/6h	2mg/kg bolus + 0.5 mg/kg/day 6/6h
ALI/ARDS days	6 to 22	16	≥ 7	15 (5 to 44)	9.7 ± 0.7	> 8 days	9.2	G1- 9.4 ± 2 G2-16.6 ± 2.7
Treatment duration (days)	21 to 42	21.3	36	8 (3-19)	27	7	Up to 32	Up to 25
Tapering	Yes	Yes	Yes, after extubation	Yes	Yes, 23 days from 4th to 27th day ↓±25% 3/3d until 14th, and then slower	Yes	Yes In 17 days from 15th to 32nd day	Yes, 4 days from the 21st day if patient still under MV 2 days from extubation if less than 21 days MP
Mean MV (days)	NR	NR	NR	NR	MP x P =	NR	MP x P 11.5 x 23 (p=0.001)	MP x P 14 x 24 (p=0.0006)
MV-free days	NR	NR	NR	NR	NR	NR	NR	28th day MP x P 11.2 x 6.8 (p<0.001)
LIS 7th to 10th day	NR	↓	↓	=	NR	↓	MP x P 1.7 x 3 (p<0.001)	NR
PaO_2/FiO_2 7th to 10th day	NR	↑	↑	=	↑	↑	MP x P 262 x148 (p<0.001)	NR
MOD score 7th to 10th day	NR	NR	NR	=	↓	↓	MP x P 0.7 x 1.8 (p<0.001)	NR
Mean ICU length of stay (days)	NR	NR	NR	NR	MP x P =	NR	NR	MP x P 17 x 20 (p=0.29)
VAP incidence (%)	NR	NR	NR	NR	NR	NR	MP x P 37 x 12 (p=0.23)	MP x P 7 x 15 (p=0.05)
In-hospital mortality (%)	20	17	28	MP x P 38 x 67 (p=0.117)	30 days MP x P 18.75 x 20 (p=0.82)	MP x P 42.9 x73.5 (p<0.05)	MP x P 12 x 62 (p=0.003)	MP x P G1- 36 x 27 (p=0.26) G2- 8 x 35 (p=0.02) Overall-29 x 29 (p=1.0)
CRP	NR	NR	NR	MP x P =	↓	NR	NR	NR

RCT – randomized clinical trial; MP – methylprednisolone; P – placebo; MV – mechanical ventilation; NR – not reported; VAP – ventilation-associated pneumonia; MOD – multiple-organ dysfunction; CRP – C reactive protein; ICU –intensive care unit. G1 – group of patients admitted to the trial with 7 – 13 days ARDS. G2 – group of patients admitted to the trial with ≥ 14 days ARDS. *Mean PICU length of stay for survivals.

ity. These effects may also have been lost because some cautions were not taken into account: drug tapering after extubation (2 days), infection surveillance and the use of neuromuscular blockers. These aspects are relevant to prevent complications of corticosteroid therapy such as infections and prolonged muscle weakness.[19] The other 3 controlled trials[7,8,10] presented substantial mortality reductions. The three case series studies,[1,5,6] reported low mortality, similar to the controlled trials' intervention arm. Six out of seven trials investigating pulmonary and/or other organs functional variables[5-10,14] showed improvement of the analyzed variables.[5,6,8-10,14]

Table 2 displays four controlled randomized clinical trials evaluating the use of low dose corticosteroids (methylprednisolone or hydrocortisone - up to 2 mg/kg/day of MP equivalent dose) early introduced (up to the 4th day of ARDS) for prolonged time (≥ 7 days in three trials[11-13] and 28 days in one trial).[15] All four trials showed significant mortality reductions and improvement of pulmonary and end-organ function variables. Meduri et al. implemented an infection surveillance program and found that 56% of nosocomial infections were seen in afebrile patients.[15] Infection incidence was significantly reduced in methylprednisolone treated pa-

Table 2 – Low-dose corticosteroids in early ALI/ARDS

Author	Lee [12] 2005	Confalonieri [11] 2005	Annane [13] 2006	Meduri [15] 2007
Study type	Controlled open-label clinical trial Historical control (1 center in Korea)	Multi-center RCT (6 centers in Italy)	Multi-center RCT (19 centers in France)	RTC (5 centers in US)
Patients number	20	46	177	91
Drug/dose	MP 2mg/kg bolus + 2mg/kg/day 6/6h	HC 200mg bolus +10mg/kg/h	HC 50mg/kg/dose 6/6h + FC 5 µg/day	MP 1 mg/kg/day 6/6h
ALI/ARDS Days	4.4	0	0	3
Treatment duration (days)	9.5	7	7	Up to 28
Tapering	Yes Starting with oral MP after ~4 days IV MP after dyspnea improvement and X-ray	No	No	Yes after 7 days
MV duration (days)	NR	MP x P 5 x 13 (p=0.09)	MP x P 23.1 x 24.9 (p=0.089)	MP x P 5 x 9.5 (p=0.002)
MV-free Days	NR	On 8th day MPxP = 4x0 (p=0.01)	MP x P 5.7±8.6 x 2.6±6.6 (p=0.089) Non-responsive	On 28th day MP x P = 16.5 x 8.7 (p=0.001)
LIS 7th to 10th day	NR	NR	NR	MP x P (p=0.004)
PaO_2/FiO_2 7th to 10th day	↑	MP x P 332 x 237 (p=0.0008)	↑ > MP group Non-responsive	MP x P 256 x 179 (p<0.006)
MOD score 7th to 10th day	NR	MP x P 0.3 x 1 (p=0.003)	NR	MP x P 0.9 x1.9 (p=0.002)
Mean PICU length of stay (days)	1.5 x 19.5	MP x P 10 x 18 (p=0.01)	NR	MP x P 7 x 14.5 (p=0.007)
VAP incidence (%)	NR	MP x P 0 x 13 (p=0.23)	MP x P 5 x 4	MP x P 14 x 57 (p=0.004)
In-hospital mortality (%)	MP x P 8 x 88	MP x P 0 x 30 (p=0.009)	On 28th day MP x P 53 x 77 (p=0.18) Non-responsive	MP x P 24 x 43 (p=0.07)
CRP	NR	MP x P 18 x 34 (p=0.01)	NR	MP x P 2.9 x 13.1 (p<0.0001)

RCT – randomized clinical trial; MP – methylprednisolone; HC – hydrocortisone; P – placebo; MV – mechanical ventilation; NR – not reported; MOD – multiple-organ dysfunction; VAP – ventilation associated pneumonia; CRP – C reactive protein; PICU – pediatric intensive care unit.

tients (p = 0.0002). Confalonieri et al.[11] analyzed the impact of corticosteroid therapy on patients with severe community acquired pneumonia and hypoxemia ($PaO_2/FIO_2 \leq 200$). Since these patients were not necessarily diagnosed as ALI/ARDS, the inclusion of this paper in meta-analysis has been criticized. Annane et al.[13] conducted a *post hoc* analysis of 177 ARDS patients, selected out of 300 patients included in a trial on the use of hydrocortisone in septic shock patients. In this study, patients were characterized as either responsive or non-responsive to a corticotrophin test before intervention. The *post hoc* analysis has shown that early low dose hydrocortisone therapy, for 7 days, was associated with better outcomes in non-responsive ARDS patients. This effect was not found in responsive ARDS patients or in non ARDS patients.

Three studies in table 2 used a less prolonged therapy course, even though effective.[11-13] This is an important issue in pediatric trial design. Concerns about prolonged use of corticosteroids in children are responsible for caution in pediatric trials. In addition to the adverse effects observed in adults, possible effects on somatic growth should be considered in children.

Meta analysis review

Five meta analysis have recently investigated the use of corticosteroids in ARDS.[17-21] Two of them (Agarwal et al.[17] and Peter et al.[18]) gathered very heterogeneous trials, with variable dose, introduction time and treatment duration schedules, considered critical aspects for drug effectiveness.

The first meta analysis conclusions,[17] which included trials on early[2,12,13] and late[7,8,14] ARDS , were not favorable to corticosteroids use in both phases. The second meta analysis included trials on prophylactic and therapeutic use of corticosteroids in ARDS .[2,8,13-15] It was concluded that therapeutic use reduced mortality and increased mechanical ventilation free-days, while prophylactic approach increased ARDS incidence.

The other three meta analysis [Meduri et al. (2008),[19] Tang et al. (2009)[20] and Meduri et al. (2009)[21]] included trials on the prolonged use of low dose corticosteroids in either early or late ARDS. Drug introduction time and therapy duration widely varied, but conclusions were favorable to corticosteroids use in ARDS.

Meduri et al. (2008)[19] included five randomized clinical trials (RCT) (n=518)[8,11,13-15] reporting significant gas exchange improvement, inflammatory markers reduction, increase in mechanical ventilation free-days and reduction in ICU length of stay. Two smaller trials showed significant reduction in the relative risk of death. Three subsequent larger trials, when combined, failed to show the same magnitude of results. However, a distinctive reduction in the relative risk of death was observed in a larger group of patients (n=400) treated before the 14th day of ARDS (38% versus 52.5%; p=0.02). The prolonged corticosteroid therapy resulted in significant improvement in patient-related variables

Tang et al. (2009)[20] selected five cohort studies (n=307)[7,9,10,12,13] and four RCT (n=341)[8,11,14,15] and showed a trend to reduction in mortality (Figure 1) as well a decrease in mechanical ventilation free-days, ICU length of stay, MOD score, lung injury score (LIS) and PaO_2/FiO_2. No increase was observed in infections, neuromyopathies or any other severe complications. The selected trials were widely heterogeneous, but meta-regression analysis showed that heterogeneity had little impact on treatment efficacy. It was concluded that the use of low dose corticosteroids was associated with improved mortality and morbidity, without increase in adverse reactions. The consistency of results in both study designs and all outcomes suggests that corticosteroids are an effective treatment for ALI/ARDS.

The second meta analysis of Meduri et al.(2009)[21] included eight controlled trials (n=628)[7-11,13-15], which demonstrated a significant reduction in systemic inflammatory markers, pulmonary dysfunction and other organs scores, duration of mechanical ventilation and ICU length of stay. A significant increase in the number of mechanical ventilation free-days and ICU free-days until day 28 were reported. These effects were three fold greater than those observed with protective low tidal volume ventilation or conservative fluid management strategy.

As shown in figure 2, there was a substantial reduction in mortality for all patients, as well as for patients treated before day 14.

Recommendations for diagnosis and management of corticosteroid insufficiency in critically ill adult patients from an international task force,[31] included treatment of ARDS with prolonged corticosteroids infusion (recommendation Grade 2B) as follows:

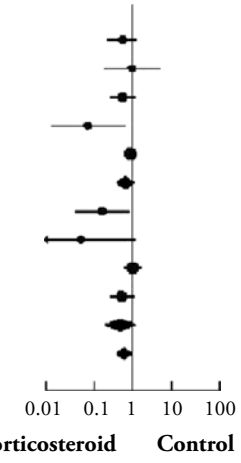
1. Early severe ARDS ($PaO_2/FiO_2 \leq 200$ with PEEP 10 cmH_2O)
2. Before day 14 in unresolving ARDS

To minimize serious risks of complications during corticosteroid therapy for ARDS, Meduri et al.[21] recommended the incorporation of secondary prevention mea-

Corticosteroids in ARDS **Endpoint:** Mortality

Study	Design	Corticosteroid n/N	Control n/N	RR (fixed) (95% CI)	Relative risk (%)	RR	p
Kee et al[7]	Cohort	5/13	12/18		19.39	0.58 (0.27-1.24)	0.16
Varpula et al[9]	Cohort	3/16	3/15		7.56	0.94 (0.22-3.94)	0.93
Huh et al[10]	Cohort	6/14	25/34		23.70	0.58 (0.31-1.10)	0.10
Lee et al[12]	Cohort	1/12	7/8		4.65	0.10 (0.01-0.63)	0.02
Annane et al[13]	Cohort	54/85	67/92		44.69	0.87 (0.71-1.07)	0.19
Subtotal		69/140	114/167			0.66 (0.43-1.02)	0.06
Meduri et al[8]	RCT	2/16	5/8		18.05	0.20 (0.05-0.81)	0.02
Confalonieri et al[11]	RCT	0/23	7/23		6.40	0.07 (0.00-1.10)	0.06
Steinberg et al[14]	RCT	28/89	29/91		40.13	0.99 (0.64-1.52)	0.95
Meduri et al[15]	RCT	15/63	12/28		35.42	0.56 (0.30-1.03)	0.06
Subtotal		45/191	53/150			0.51 (0.24-1.09)	0.08
Total						0.62 (0.43-0.91)	0.01

Heterogeneity test: p=0.039; I^2 = 51%
Total effect test: Z = 2.88 (p=0.004)



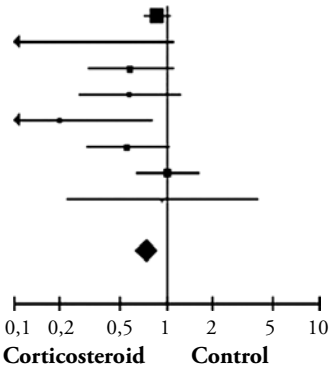
RCT – randomized clinical trial; CI – confidence interval; RR – relative risk. Modified from Tang et al., 2009.[20]

Figure 1 – Corticosteroid effect on mortality. The markers size is proportional to each trial weight.

Corticosteroids in ARDS **Endpoint:** Mortality

Studies	Corticosteroid n/N	Control n/N	Relative weight	RR MH. fixed. 95%CI	RR (fixed) MH. fixed. 95%CI
Annane et al[13]	54/85	67/92	43.3%	0.87 (0.71-1.07)	
Confalonieri et al[11]	0/23	7/23	5.0%	0.07 (0.00-1.10)	
Huh et al[10]	6/14	25/34	9.8%	0.58 (0.31-1.10)	
Kee et al[7]	5/13	12/18	6.8%	0.58 (0.27-1.24)	
Meduri et al[8]	2/16	5/8	4.5%	0.20 (0.05-0.81)	
Meduri et al[8]	15/63	12/28	11.2%	0.56 (0.30-1.03)	
Steinberg et al[14]	26/89	26/91	17.3%	1.02 (0.65-1.62)	
Varpula et al[9]	3/16	3/15	2.1%	0.94 (0.22-3.94)	
Total (IC 95%)	11/319	157/309	100.0%	0.75 (0.63-0.89)	

Heterogeneity test: χ^2=12.33; gl=7(P=0.09). I^2 =43%
Total effect test: Z = 3.31 (p=0.0009)



M.H. RR – relative risk estimated by Mantel-Haenszel method; CI – confidence interval. Modified from Meduri, 2009.[21]

Figure 2 – Prolonged corticosteroid treatment effect on survival.

sures including: 1) continuous corticosteroid infusion to prevent glycemic fluctuations; 2) avoidance of neuromuscular blockers to minimize risk of muscle weakness; 3) avoidance of etomidate, which inhibits corticosteroids synthesis; 4) strict infection surveillance with cultures of weekly respiratory secretion samples in addition to strict infection diagnosis criteria; and 5) tapering of corticosteroid doses (9 to 12 days) to allow GCR number and hypothalamic-pituitary-adrenal axis to recover and prevent inflammatory rebound.

Corticosteroids adverse effects

Ten per cent of the children are estimated to make use of corticosteroids at any time during childhood. One of the most feared adverse effects in children is growth suppression, associated with continued or repeated corticosteroids use in chronic diseases. This effect is both dose and time-dependent, and predominantly occurs during the first six months of treatment. The bone metabolism and stature impairment come from several mechanisms: suppression of bone marrow osteoblastogenesis increase in bone reabsorption, increase in renal and intestinal calcium loss with secondary hyperparathyroidism, inhibition of growth hormone secretion and activity, direct effect on growth plate, and change in gonadal function from direct or indirect action on hypothalamic-pituitary-adrenal axis. Osteopenia was reported in children receiving doses of prednisolone lower than 0.16 mg/kg/day.[40]

Another concern, both in adults and children, is the hypothalamic-pituitary axis suppression, with consequent adrenal insufficiency following drug discontinuation. It is recommended in the literature that therapy courses longer than seven days are followed by drug tapering, a widely used method for the management of acute bronchial hyperreactivity associated respiratory diseases. Recommendations for dose tapering after prolonged low dose methylprednisolone infusion for ARDS therapy not only preclude inflammation rebound effect but also prevent adrenal insufficiency.

Acute neuromuscular dysfunction associated with critical illnesses is frequently mentioned in adult intensive care. The incidence ranges from 32% to 100% in patients ventilated longer than 3 days, depending on the population studied.[41] An association between this complications and corticosteroids therapy is suspected, mainly when neuromuscular blockers (NMB) are concomitantly used. However, evidence suggest that systemic inflammation is implied in the pathogenesis of this dysfunction. The beneficial effects of corticosteroid therapy on several pulmonary function variables, including reduction in duration of mechanical ventilation contradict this association. A recent review[42] of this issue in critically ill children revealed lack of data on risk factors, incidence, natural history and prognosis of this entity in childhood. Data from 34 pediatric patients showed that twenty patients had sepsis and systemic inflammatory response, nine were admitted after bone marrow or solid organ transplantation, and five for asthma.[42] One single prospective series on neuropathy in critically ill children reported a 1.7% incidence (14/830 ICU patients).[43] In the absence of evidence supporting preventive recommendations in children, it seems reasonable to comply with adult patients' recommendations to avoid concomitant use of NMB and corticosteroids.

Finally, recent trials have not confirmed the suspected increase on the risk of nosocomial infection.[11,13-15] Apparently prolonged low dose corticosteroids therapy has an immunomodulator effect by improving innate immunity.[44] However, corticosteroids may mask signs and symptoms of infection by suppressing fever and leucocytosis induction. Infection surveillance with periodic cultures of respiratory and other relevant body fluid specimens is critical during treatment course.[15,44,45]

Blood glucose and blood pressure monitoring, in addition to the use of H2 blockers or proton pump inhibitors are other measures routinely used in intensive care patients, which also prevent other corticosteroids complications (hyperglycemia, arterial hypertension, gastritis), providing both prophylaxis and early intervention.

Design adaptation for a pediatric trial

A study design that is adequate for pediatric population needs some ajustments. Diagnosing ALI/ARDS in children is challenging. The clinical and radiological criteria recommended by the American-European consensus have low sensitivity and specificity even for adults. In addition to these difficulties, there are those peculiar to pediatric age. Difficult radial artery catheterization in some children renders PaO_2/FiO_2 ratio a complicated criterion for early syndrome diagnosis and follow-up. PaO_2 via artery puncture causes intensive pain and crying that result in temporary drop of both PaO_2 and SpO_2. The use of the SpO_2/FiO_2 ratio in ADRS diagnosis was recently described in two trials, one of them in pediatrics.[46,47] The non-invasive SpO_2 measurement spares arterial puncture and either systemic or topic analgesia, and is an excellent resource to overcome this issue.

Another pediatric issue is the difficulty to conduct frequent bronchoscopies for nosocomial pneumonia surveillance and inflammatory markers measurements. The use of quantitative tracheal aspirate cultures was shown to be appropriate for monitoring purposes and appropriate antibiotic therapy of nosocomial pneumonias.[48]

Meduri et al. used a 28-day course of methylprednisolone to treat ARDS[15] However, concerns about osteoarticular, hormonal and immunological effects of prolonged corticosteroid administration and evidences of beneficial effects with shorter courses discussed in this review, make a 14-day course of methylprednisolone (seven days with the starting dose and seven dose taper-

ing days) a more appropriate schedule to be investigated in a pediatric pilot trial.

Finally, the lower mortality of ALI/ARDS in children precludes the use of mortality as a primary endpoint in pediatric trials, as very large samples would be required. Pulmonary variables (such as LIS improvement and duration of mechanical ventilation) and other organ function variables (improvement of multiple organ dysfunction score) are more feasible and appropriate for initial trials with smaller samples.

CONCLUSION

Extensive literature is available concerning the use of corticosteroids early and late in the course of ALI/ARDS with evidence of beneficial effects in adults. Randomized trials on the use of corticosteroid therapy in pediatric ALI/ARDS are missing. Nevertheless, corticosteroids are widely used in pediatric respiratory diseases. Lower incidence, shorter duration of mechanical ventilation, lower mortality, the difficulties to recognize ALI/ARDS in children sometimes masked by more frequent underlying diagnosis (bronchiolitis, sepsis, pneumonia) renders pediatric trials challenging. The efficacy and safety of this therapy in children, as well as the impact of corticosteroid on morbidity and mortality, need to be elucidated.

Based on clinical and experimental studies, in pediatric trials it is suggested to use: 1) SpO_2/FiO_2 ratio for ARDS diagnosis and follow-up; 2) the choice of primary endpoints other than mortality, such as: pulmonary functional variables (LIS improvement and mechanical ventilation time); 3) and the use of multiple organ dysfunction score, ICU length of stay and serum inflammation markers as secondary endpoints. Considering children's peculiarities, some questions must be approached in a pediatric study design: 1) Lower ARDS mortality rate in pediatrics comes from reduced inflammatory response as compared to the adult; 2) Early (≤ 72 hours) versus late corticosteroid administration in children's ARDS allows a shorter course without loosing benefits; 3) A total 14 days methylprednisolone course, with a starting dose of 1 mg/kg/day dose followed by continued 1 mg/kg/day infusion for the first 7 days and then dose tapering (50% of the previous dose every 2 days for additional 7 days until discontinuation) is safe and effective in children?

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RESUMO

A terapia com corticosteroide na lesão pulmonar aguda e na síndrome do desconforto respiratório agudo é um dos temas mais controversos na literatura. Apesar de o corticosteroide ser amplamente utilizado na faixa etária pediátrica, os estudos com corticosteroide na lesão pulmonar aguda/síndrome do desconforto respiratório agudo são restritos a adultos. Esse artigo realiza uma revisão crítica dos estudos experimentais e clínicos sobre a utilização de corticosteroide na síndrome do desconforto respiratório agudo, procurando apontar os prováveis riscos e benefícios da sua utilização em pediatria. Para tal, foi realizada ampla revisão da literatura, de 1980 a 2010, incluindo artigos experimentais e clínicos, bem como metanálises, usando-se o banco de dados do Medline, Registro Central da Cochrane de ensaios clínicos controlados, banco de dados de revisões sistemáticas da Cochrane, SciELO, LILACS e BIREME. As palavras chaves utilizadas foram: lesão pulmonar aguda, síndrome do desconforto respiratório agudo, corticosteroides, criança, ensaios clínicos, metanálises, revisões e relato de casos. A corticoterapia na lesão pulmonar aguda/síndrome do desconforto respiratório agudo foi associada à redução da resposta inflamatória sistêmica, melhora da oxigenação e da disfunção orgânica múltipla, diminuição do tempo de ventilação mecânica e dos dias de internação nas unidades de terapia intensiva. Sugere-se, para pacientes pediátricos, o uso precoce (nas primeiras 72h) e prolongado (por 14 dias) de metilprednisolona na lesão pulmonar aguda/síndrome do desconforto respiratório agudo, com dose de 1 mg/kg/dia sob infusão contínua para evitar variabilidade glicêmica e recomenda-se controle rígido da existência de infecção. Propõe-se a adequação de alguns aspectos do diagnóstico, da intervenção e da seleção de desfechos para viabilizar os estudos em pediatria. É fundamental a realização de mais pesquisas para elucidar a segurança e eficácia da administração de metilprednisolona na lesão pulmonar aguda/síndrome do desconforto respiratório agudo em crianças, bem como estabelecer os melhores parâmetros a serem utilizados no diagnóstico e acompanhamento da doença, na monitorização das complicações da corticoterapia, bem como os desfechos primários mais adequados.

Descritores: Lesão pulmonar aguda; Síndrome do desconforto respiratório do adulto; Corticosteroides; Criança; Ensaios clínicos; Metanálises

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