Effects of nebulized epinephrine in association with hypertonic saline for infants with acute bronchiolitis: a systematic review and meta-analysis

Renan Pereira<sup>1</sup>, Versiéri Almeida<sup>1</sup>, Mariana Zambrano<sup>1</sup>, Linjie Zhang<sup>2</sup>, and Sérgio Amantéa<sup>1</sup>

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## Abstract

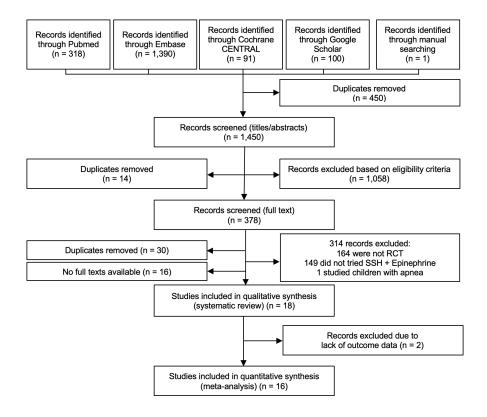
Management of acute bronchiolitis remains controversial due to lack of strong evidence-based data. Nebulized epinephrine and hypertonic saline have been studied in infants with bronchiolitis, with conflicting results. This systematic review and meta-analysis aimed to evaluate the efficacy on length of stay (LOS), clinical severity scores (CSS), oxygen saturation (SaO2) and safety profile of nebulized epinephrine plus hypertonic saline (HS) in infants with acute bronchiolitis. Outcomes were represented by mean differences (MD) or standard mean differences (SMD) and 95% confidence intervals (CIs) were utilized. 18 trials were systematically selected and 16 of them contributed for the meta-analysis (1,756 patients). Overall, a modest but significant positive impact was observed of the combination therapy on LOS (MD of -0.35 days, 95% CI -0.62 to -0.08, p = 0.01, I2 = 91%). Stratification by time of CSS assessment unveiled positive results in favor of the combination therapy in CSS assessed 48 hours and 72 hours after the admission (SMD of -0.35, 95% CI -0.62 to -0.09, p = 0.008, I2 = 41% and SMD of -0.27, 95% CI -0.50 to -0.04, p = 0.02, I2 = 0%, respectively). No difference in SaO2 was observed. Additional data showed a consistent safety profile, with a low rate of adverse events (1%), most of them mild and transient. In conclusion, nebulized epinephrine plus HS may be considered as a safe, cheap and efficient alternative for decreasing LOS and CSS in infants with acute bronchiolitis, especially on those who require more than 48 hours of hospitalization.

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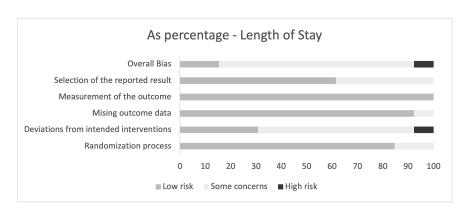
<sup>&</sup>lt;sup>1</sup>Universidade Federal de Ciências da Saúde de Porto Alegre

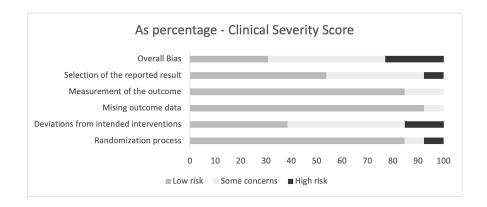
<sup>&</sup>lt;sup>2</sup>Universidade Federal do Rio Grande

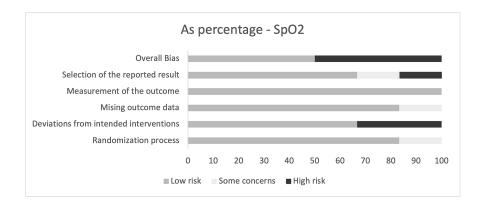


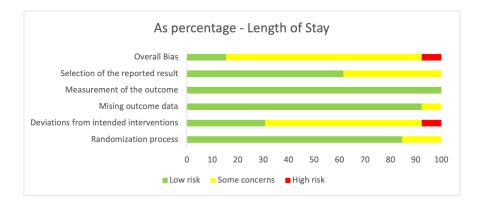
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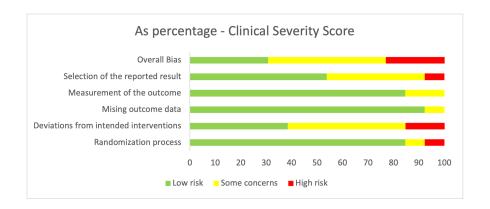
TABLE 1 Characteristics of included studies.pdf available at https://authorea.com/users/414005/articles/522155-effects-of-nebulized-epinephrine-in-association-with-hypertonic-saline-for-infants-with-acute-bronchiolitis-a-systematic-review-and-meta-analysis

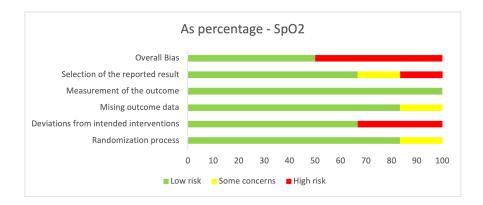


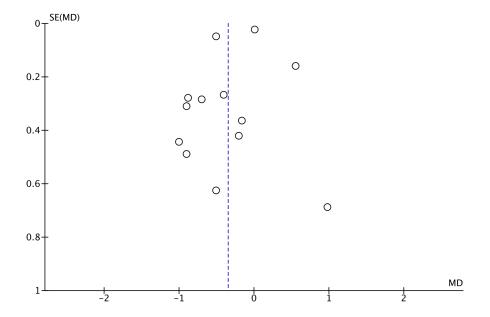


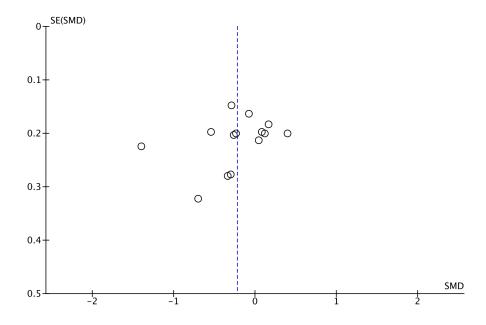








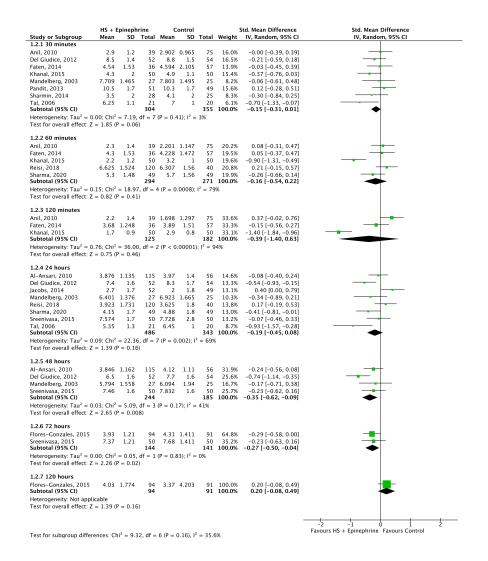




	SSH +	SSH + Epinephrine			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Al-Ansari, 2010	1.48	1.39	115	1.88	1.76	56	8.7%	-0.40 [-0.93, 0.13]	<del></del>
Campaña, 2014	4.5	2.22	42	5	2.96	32	3.5%	-0.50 [-1.73, 0.73]	· · · · ·
Del Giudice, 2012	4.9	1.3	54	5.6	1.6	52	8.4%	-0.70 [-1.26, -0.14]	<del></del>
Faten, 2014	4.48	3.81	36	3.5	1.973	57	3.0%	0.98 [-0.37, 2.33]	<del></del>
Flores-Gonzales, 2015	3.94	1.37	94	4.82	2.3	91	8.5%	-0.88 [-1.43, -0.33]	<del></del>
Jacobs, 2014	0.17	0.0037	52	0.162	0.166	49	13.1%	0.01 [-0.04, 0.05]	+
Mandelberg, 2003	3	1.2	27	4	1.9	25	5.5%	-1.00 [-1.87, -0.13]	<del></del>
Pandit, 2013	3.92	1.72	51	4.08	1.9	49	6.8%	-0.16 [-0.87, 0.55]	<del></del>
Reisi, 2018	1.841	0.604	90	1.283	0.796	30	11.2%	0.56 [0.25, 0.87]	-
Sharma, 2020	3.858	2.029	49	4.058	2.138	49	5.8%	-0.20 [-1.03, 0.63]	<del></del>
Sreenivasa, 2015	2.5	1.4	50	3.4	1.7	50	7.8%	-0.90 [-1.51, -0.29]	<del></del>
Tal, 2006	2.6	1.4	21	3.5	1.7	20	4.9%	-0.90 [-1.86, 0.06]	
Uysalol, 2017	0.166	0.246	75	0.666	0.617	231	12.9%	-0.50 [-0.60, -0.40]	
Total (95% CI)			756			791	100.0%	-0.35 [-0.62, -0.08]	•
Heterogeneity: $Tau^2 = 0.14$ : $Chi^2 = 132.83$ , $df = 12$ (P < 0.00001): $I^2 = 91\%$									
Test for overall effect: $Z = 2.56 (P = 0.01)$								-2 -1 0 1 2	
									Favours HS + Epinephrine Favours Control

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TABLE 2 LOS subgroup analysis.pdf available at https://authorea.com/users/414005/articles/522155-effects-of-nebulized-epinephrine-in-association-with-hypertonic-saline-for-infants-with-acute-bronchiolitis-a-systematic-review-and-meta-analysis



Mean Difference HS + Epinephrine Control SD Total Mean SD Total Weight IV, Random, 95% CI Study or Subgroup 1.10.1 30 minutes IV, Random, 95% CI 97.8 1.8 36 97.95 1.973 93.8 0.8 50 94.2 2 93.2 3.75 51 92.55 4 96.9 1 28 96.7 1.4 75 24.9% -0.15 [-0.89, 0.59] 50 38.1% -0.40 [-1.00, 0.20] 49 5.9% 0.65 [-0.87, 2.17] 25 31.0% 0.20 [-0.46, 0.86] 199 100.0% -0.09 [-0.46, 0.28] Anil, 2010 Khanal, 2015 Pandit, 2013 Sharmin, 2014 Subtotal (95% CI) Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 2.71, df = 3 (P = 0.44);  $I^2$  = 0% Test for overall effect: Z = 0.48 (P = 0.63) 1.10.2 60 minutes 98.5 1.2 36 98.5 1.54 75 31.8% 0.00 [-0.52, 0.52] 94.9 0.9 50 95.8 1.1 50 33.6% -0.90 [-1.29, -0.51] 93.58 3.916 120 92.433 3.9 40 18.1% 1.15 [-0.25, 2.54] 91.4 3.8 49 90.8 3.9 49 16.5% 0.60 [-0.92, 2.13] 255 214 100.0% 0.00 [-0.84, 0.84] Anil, 2010 Khanal, 2015 Reisi, 2018 Sharma, 2020 Subtotal (95% CI) Subtotal (95% cl) 253 Heterogeneity: Tau<sup>2</sup> = 0.51; Chi<sup>2</sup> = 14.68, df = 3 (P = 0.002); l<sup>2</sup> = 80% Test for overall effect: Z = 0.01 (P = 0.99) 1.10.3 120 minutes \$1.10.3 120 minutes \$\$ Annil, 2010 98.5 1.2 36 98.7 1.2 75 49.3% -0.20 [-0.68, 0.28] \$\$ Khanal, 2015 95.6 1 50 97 1 50 50.7% -1.40 [-1.79, -1.01] \$\$ Subtotal (95% CI) 86 125 100.0% -0.81 [-1.98, 0.37] \$\$ Heterogeneity: Tau' = 0.67; Chi' = 14.52, df = 1 (P = 0.0001);  $I^2 = 93\%$  \$\$ Test for overall effect: Z = 1.35 (P = 0.18) 1.10.4 24 hours Reisi, 2018 95.202 3.855 120 94.52 3.9 40 100.0% 0.68 [-0.71, 2.07]
Subtotal (95% CI) 120 40 100.0% 0.68 [-0.71, 2.07] Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34) Favours HS + Epinephrine Favours control