NEBULISED $MgSO_4$ IN ACUTE SEVERE ASTHMA IN CHILDREN

Dr. Đỗ THƯƠNG HOÀI
Dr. LÊ HỒNG HÀ

RESPIRATORY DEPARTMENT 2

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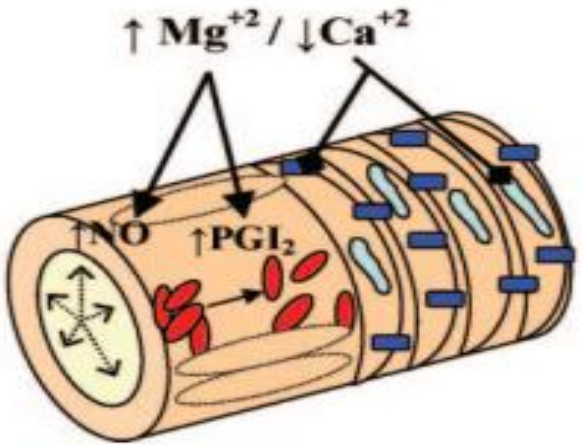
I. OVERVIEW

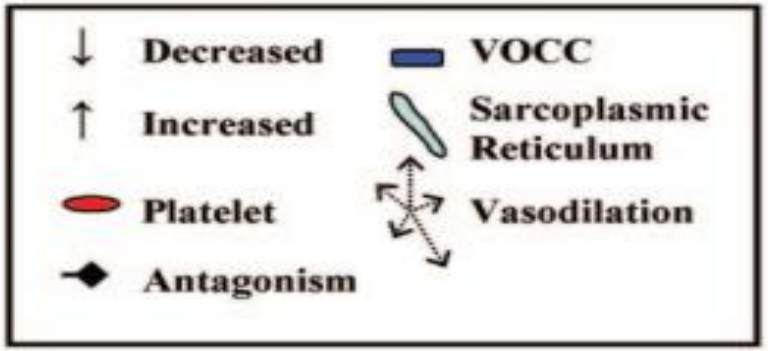
- Acute asthma = main reason for acute hospital admission in children.
- Initial management in children = inhaled β2-agonists + ipratropium + systemic corticosteroids.
- Worsening / exacerbations asthma : aminophylline, $MgSO_4$, adrenaline …….
- $MgSO_4$ = resistant to standard therapy. Adverse effect = hypotension.
- Nebulized $MgSO_4$

I. OVERVIEW

Vascular Effects of Magnesium Sulfate.

Cellular Target	Mode of Action	Possible Mechanism(s)
Smooth Muscle Uterine +++ Mesenteric +++ Aorta +++ Cerebral +	Relaxation ↓ Vasodilation ↓ Decreased Vascular Resistance	Calcium Antagonism Decreased Voltage-operated Calcium Channel (VOCC) Activity Decreased $[Ca^{+2}]_i$ Release From Sarcoplasmic Reticulum
Endothelium	Decreased Platelet Aggregation	Increased Prostaglandin I_2 (PGI_2)
	Vasodilation	Increased Nitric Oxide (NO, Gestation Dependent)





I. OVERVIEW

Respiratory tract :

- Bronchodilator = blocks ca^{2+} intracellular/ inhibition binding calci and myosin results in muscle cell relaxation.
- Inhibiting acetylcholine release.
- Inhibiting histamin release from mastocell.
- Anti-inflammatory = stabilizes T cells, neutrophil respiratory burst.

The use og MgSO4 in brochial asthma , anata kowal et al 2006

British Thoracic Society (BTS), Scottish Intercollegiate Guidelines Network (SIGN). British Guideline on the Management of Asthma. A national clinical guideline. London: BTS; revised May 2011.

II. RESEARCHES

Respiratory Medicine (2013) 107, 321–330

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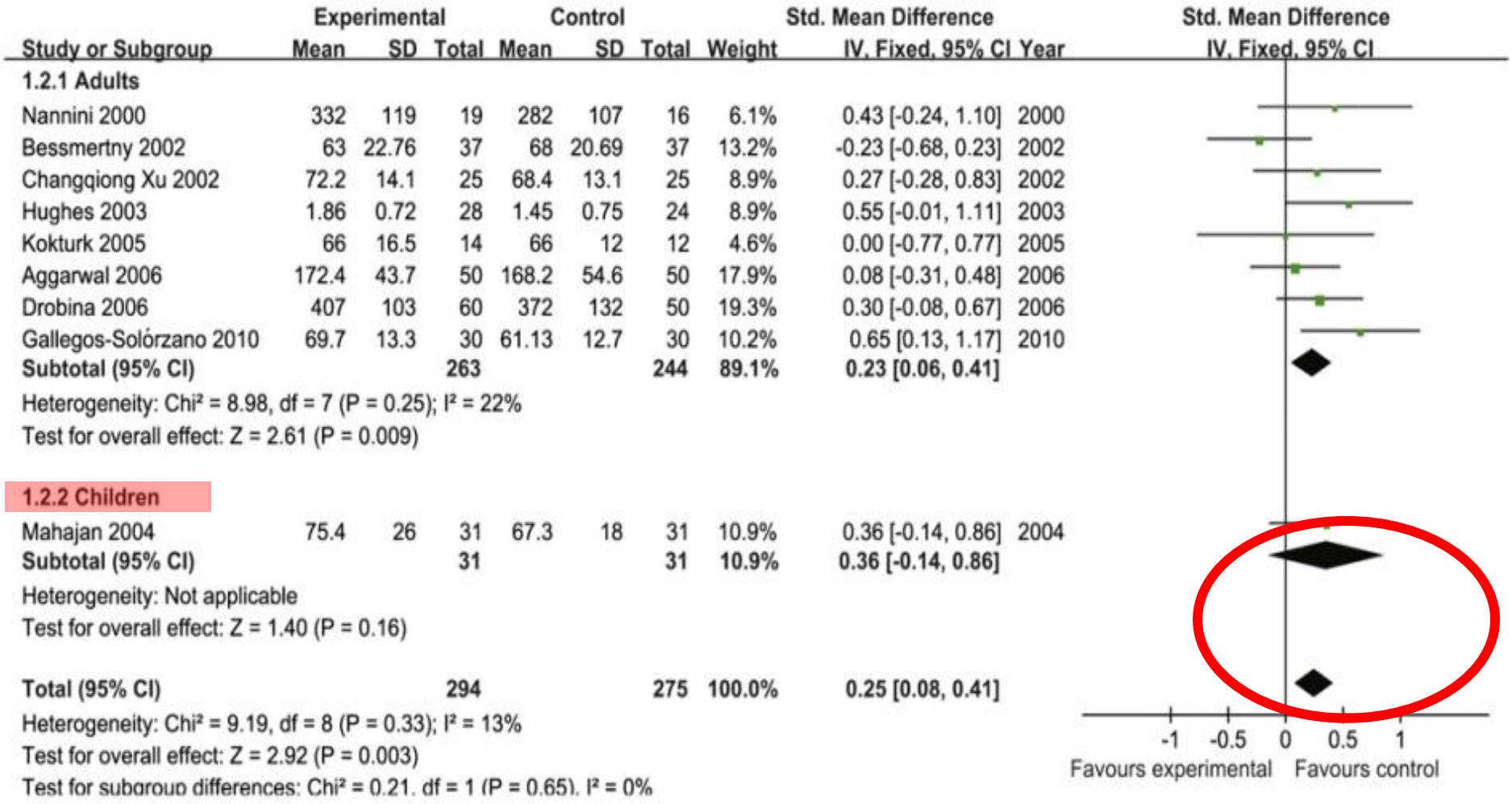
REVIEW

Intravenous and nebulized magnesium sulfate for treating acute asthma in adults and children: A systematic review and meta-analysis

Zhilei Shan [a,b], Ying Rong [a,b], Wei Yang [a,b], Di Wang [a,b], Ping Yao [a,b], Jungang Xie [c,*], Liegang Liu [a,b,**]

II. RESEARCHES



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
1.2.1 Adults									
Nannini 2000	332	119	19	282	107	16	6.1%	0.43 [-0.24, 1.10]	2000
Bessmertny 2002	63	22.76	37	68	20.69	37	13.2%	-0.23 [-0.68, 0.23]	2002
Changqiong Xu 2002	72.2	14.1	25	68.4	13.1	25	8.9%	0.27 [-0.28, 0.83]	2002
Hughes 2003	1.86	0.72	28	1.45	0.75	24	8.9%	0.55 [-0.01, 1.11]	2003
Kokturk 2005	66	16.5	14	66	12	12	4.6%	0.00 [-0.77, 0.77]	2005
Aggarwal 2006	172.4	43.7	50	168.2	54.6	50	17.9%	0.08 [-0.31, 0.48]	2006
Drobina 2006	407	103	60	372	132	50	19.3%	0.30 [-0.08, 0.67]	2006
Gallegos-Solórzano 2010	69.7	13.3	30	61.13	12.7	30	10.2%	0.65 [0.13, 1.17]	2010
Subtotal (95% CI)			**263**			**244**	**89.1%**	**0.23 [0.06, 0.41]**	
Heterogeneity: Chi² = 8.98, df = 7 (P = 0.25); I² = 22%									
Test for overall effect: Z = 2.61 (P = 0.009)									
1.2.2 Children									
Mahajan 2004	75.4	26	31	67.3	18	31	10.9%	0.36 [-0.14, 0.86]	2004
Subtotal (95% CI)			**31**			**31**	**10.9%**	**0.36 [-0.14, 0.86]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.40 (P = 0.16)									
Total (95% CI)			**294**			**275**	**100.0%**	**0.25 [0.08, 0.41]**	
Heterogeneity: Chi² = 9.19, df = 8 (P = 0.33); I² = 13%									
Test for overall effect: Z = 2.92 (P = 0.003)									
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%									

Figure 4 Effect of nebulized magnesium sulfate upon respiratory function.

II. RESEARCHES

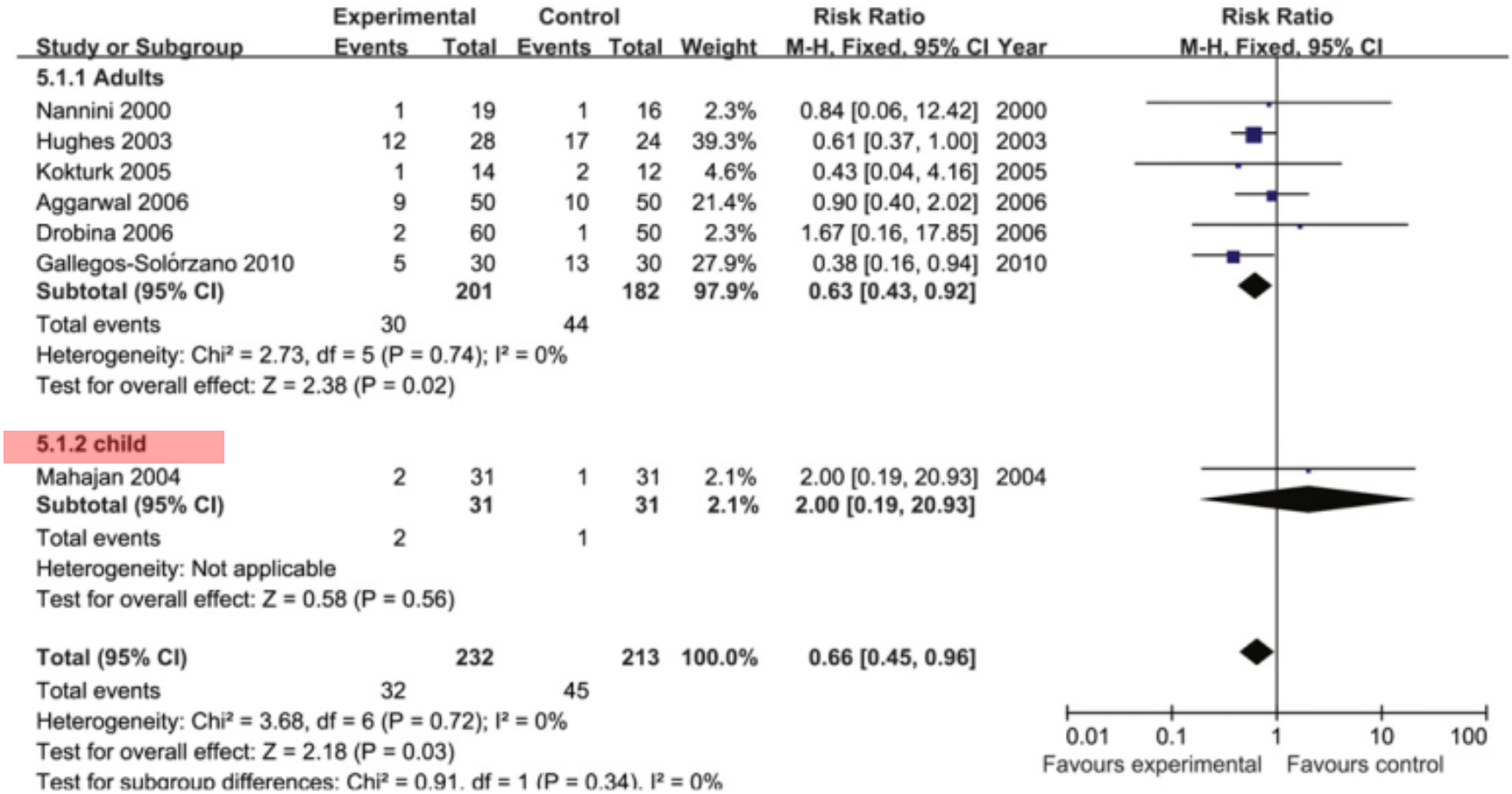


Figure 5 Effect of nebulized magnesium sulfate upon hospital admission.

Respiratory Medicine (2013) 107, 321e330

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Cochrane Database of Systematic Reviews

Inhaled magnesium sulfate in the treatment of acute asthma (Review)

Blitz M, Blitz S, Beasely R, Diner B, Hughes R, Knopp JA, Rowe BH

Citation: Blitz M, Blitz S, Beasely R, Diner B, Hughes R, Knopp JA, Rowe BH. Inhaled magnesium sulfate in the treatment of acute asthma. *Cochrane Database of Systematic Reviews* 2005, Issue 4. Art. No.: CD003898. DOI: 10.1002/14651858.CD003898.pub4.

II. RESEARCHES

Main results

Six trials involving 296 patients were included. Four studies compared nebulised $MgSO_4$ with β_2-agonist to β_2-agonist and two studies compared $MgSO_4$ to β_2-agonist alone. Three studies enrolled only adults and 2 enrolled exclusively pediatric patients; three of the studies enrolled severe asthmatics. Overall, there was a non significant improvement in pulmonary function between patients whose treatments included nebulised $MgSO_4$ in addition to β_2-agonist (SMD: 0.23; 95% CI: -0.03 to 0.50; 4 studies). Hospitalizations were similar between the groups (RR: 0.69; 95% CI: 0.42 to 1.12; 3 studies). Subgroup analyses did not demonstrate significant differences in lung function improvement between adults and children, but in severe asthmatics the lung function difference was significant (SMD: 0.55; 95% CI: 0.12 to 0.98). Conclusions regarding treatment with nebulised $MgSO_4$ alone are difficult to draw due to lack of studies in this area.

Authors' conclusions

Nebulised inhaled magnesium sulfate in addition to β_2-agonist in the treatment of an acute asthma exacerbation, appears to have benefits with respect to improved pulmonary function in patients with severe asthma and there is a trend towards benefit in hospital admission. Heterogeneity between trials included in this review precludes a more definitive conclusion.

Effect of Inhaled $MgSO_4$ on FEV1 and PEF in Children with Asthma Induced by Acetylcholine: A Randomized Controlled Clinical Trail of 330 Cases

by Y. X. Sun,[1] C. H. Gong,[2] S. Liu,[2] X. P. Yuan,[3] L. J. Yin,[3] L. Yan,[3] T. T. Shi,[2] *and* J. H. Dai[3]

[1]*Ministry of Education Key Laboratory of Child Development and Disorders*

[2]*Laboratory of Pulmonary Function Test, Children's Hospital, Chongqing Medical University*

[3]*Center of Respiratory Disorders, Children's Hospital, Chongqing Medical University, 400014, Chongqing, China*

Correspondence: J. H. Dai, No. 136, 2nd Road of Zhongshan, Yuzhong District, Chongqing, China, 400014.
E-mail <danieljh@163.com>.

Summary

Objectives: To determine the response of nebulized magnesium sulfate on the lung function of acetylcholine-induced asthma children.

Methods: Three hundred and thirty children of asthma with positive bronchial provocation test were randomly divided into three groups: magnesium sulfate, albuterol, and a combination of magnesium sulfate and albuterol. Lung function was compared between the three groups.

Results: Forced expiratory volume in one second (FEV1) and peak expiratory flow (PEF) as percentage over predicted at 10 min and 20 min in albuterol and combination group were significantly improved when compared to magnesium group. The changes in FEV1 and PEF expressed as absolute and percentage over predicted was not statistically significant from baseline to 20 min in magnesium, albuterol, and combination of magnesium sulfate and albuterol. There was no significant adverse effect observed during the present study.

Conclusion: Nebulized magnesium sulfate alone has a bronchodilatory effect in Ach-induced asthmatic children. The combination of $MgSO_4$ and albuterol did not has a synergistic effect.

Egyptian Journal of Chest Diseases and Tuberculosis (2012) 61, 29–34

The Egyptian Society of Chest Diseases and Tuberculosis

Egyptian Journal of Chest Diseases and Tuberculosis

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ORIGINAL ARTICLE

Nebulized magnesium sulphate versus nebulized salbutamol in acute bronchial asthma

E.A. Abdelnabi [a], M.M. Kamel [a,*], A.E. Ali [b]

Abstract *Aim of work:* The aim of this study is to investigate the efficacy of nebulized magnesium sulphate as a bronchodilator in acute asthma as compared to nebulized salbutamol.

Subjects and methods: This was a randomized controlled study conducted in El-Giza Chest Hospital Emergency Department between January 2010 and June 2011. Randomization was achieved by closed envelope technique. This study involved 48 known bronchial asthma patients presenting with acute or subacute exacerbations. Patients were divided into Control group (A) and Study group (B). Initial assessment of all patients included history, clinical examination (auscultation, respiratory rate (RR), heart rate (HR) and working of accessory muscles). In addition to measurement of peak expiratory flow rate (PEFR) and oxygen saturation (SO_2). Patients received standard treatment for their acute attacks in the form of Sodium hydrocortisone hemisuccinate 100 mg every 6 hours, Supplemental oxygen and nebulized bronchodilator which was salbutamol in group (A) in the form of 4 doses of nebulized solution 0.5 gm% (each dose 1 ml containing 5 mg salbutamol) twenty minutes apart and Magnesium sulphate in group (B) in the form of 4 doses of nebulized solution 10 gm% (each dose 1 ml containing 100 mg magnesium sulphate) twenty minutes apart. Reassessment of the patients was performed after 2 hours to detect improvement.

Conclusion: The use of $MgSO_4$ by nebulization in patients with acute asthma attacks results in improvement of clinical condition, increase in peak expiratory flow rate (PEFR), reduction in heart rate (HR), reduction in respiratory rate (RR) and improvement in oxygen saturation (SO_2). The increase in PEFR (bronchodilatory effect) was significantly less than that achieved in patients receiving the usual treatment with Short acting β2 agonists, e.g. salbutamol, when either agents were used alone.

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Inhaled magnesium sulfate in the treatment of acute asthma (Review)

Powell C, Dwan K, Milan SJ, Beasley R, Hughes R, Knopp-Sihota JA, Rowe BH

Powell C, Dwan K, Milan SJ, Beasley R, Hughes R, Knopp-Sihota JA, Rowe BH.
Inhaled magnesium sulfate in the treatment of acute asthma.
Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: CD003898.
DOI: 10.1002/14651858.CD003898.pub5.

$MgSO_4$ + B2-agonists versus B2-agonists alone for acute asthma

Patient or population: people with acute asthma
Settings: hospital and ED
Intervention: $MgSO_4$ + B_2-agonists
Comparison: B_2-agonists alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	B2-agonists alone	$MgSO_4$ + B2-agonists				
Pulmonary Function testing FEV1		The mean pulmonary function testing FEV1 in the intervention groups was **0.23 standard deviations higher** (0.27 lower to 0.74 higher)	SMD 0.23 (-0.27 to 0. 74)	188 (3 studies)	⊕⊕⊕○ **moderate**[1]	
Pulmonary function testing PEF - up to 60 minutes		The mean pulmonary function testing PEF- up to 60 minutes in the intervention groups was **7.07 L/min higher** (11.69 lower to 25.84 higher)	MD 7.07 [-11.69, 25.84]	135 (2 studies)	⊕⊕⊕○ **moderate**[2]	
Pulmonary function testing PEF - Discharge		The mean pulmonary function testing PEF - discharge in the intervention groups was **0.68 L/min higher**	MD 0.68 [-8.56, 9.92]	26 (1 study)	⊕⊕○○ **low** [3]	
		(8.56 lower to 9.92 higher)				
Admission to Hospital	**240 per 1000**	**182 per 1000** (117 to 278)	**RR 0.76** (0.49 to 1.16)	249 (4 studies)	⊕⊕⊕○ **moderate**[4]	Please see footnote 4
Serious Adverse Events	See comment	See comment	RD 0.00 [-0.03, 0.03]	223 (4 studies)	⊕⊕⊕○ **moderate**[5]	Risks were calculated from pooled risk differences
Mild-Moderate Adverse Events	**262 per 1000**	**233 per 1000** (123 to 343)	RD -0.03 [-0.14, 0.08]	209 (3 studies)	⊕⊕⊕○ **moderate**[6]	Risks were calculated from pooled risk differences

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Inhaled magnesium sulfate in the treatment of acute asthma (Review)

Knightly R, Milan SJ, Hughes R, Knopp-Sihota JA, Rowe BH, Normansell R, Powell C

Knightly R, Milan SJ, Hughes R, Knopp-Sihota JA, Rowe BH, Normansell R, Powell C.

Inhaled magnesium sulfate in the treatment of acute asthma.

Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD003898.

DOI: 10.1002/14651858.CD003898.pub6.

$MgSO_4$ + SABA + ipratropium compared to SABA + ipratropium in the treatment of acute asthma

Patient or population: adults and children with acute exacerbation of asthma
Setting: emergency department/inpatient
Intervention: $MgSO_4$ + SABA + ipratropium
Comparison: SABA + ipratropium

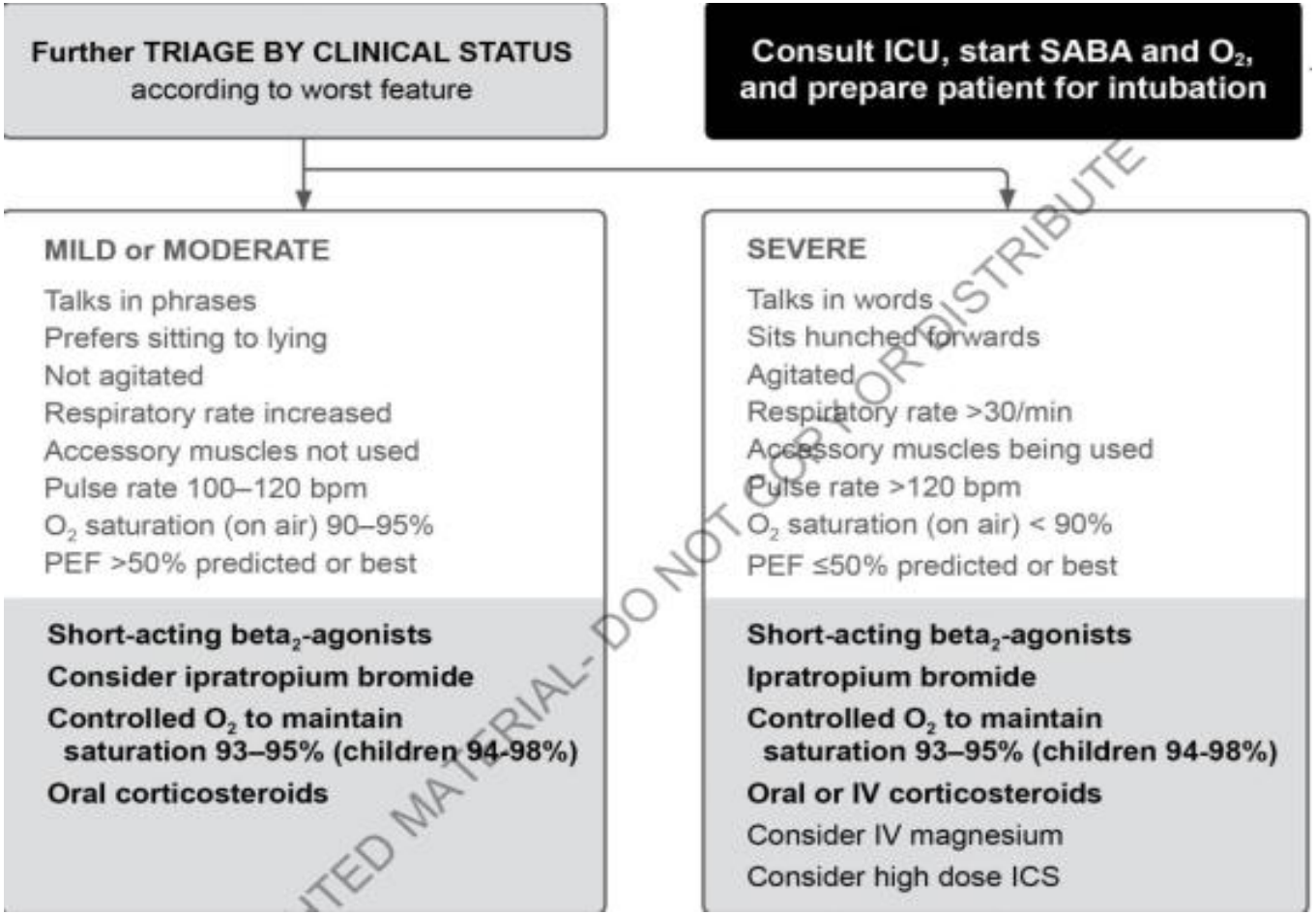
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with SABA + ipratropium	Risk with MgSO4 + SABA + ipratropium				
Pulmonary function (% predicted FEV1) (90 to 120 minutes)	The mean pulmonary function (% predicted FEV1) was 65%	% predicted FEV1 was 3.28% higher (1.06 higher to 5.49 higher)	-	120 (2 RCTs)	⊕◯◯◯ VERY LOW [123]	Outcome measured at 90 mins in 1 study and 120 mins in the other 1 study (Gaur 2008) has reported much smaller standard deviations and contributes almost 90% of analysis weight
Pulmonary function % predicted PEF (60 minutes)	The mean pulmonary function % predicted PEF was 50.45%	% predicted PEF was 0.05 higher (2.33 lower to 2.42 higher)	-	636 (2 RCTs)	⊕⊕⊕◯ MODERATE [245]	Both studies in adults Mean control group % predicted PEF was 36% in 1 study and 64.9% in the other
Clinical severity scores (60 minutes)	The mean dyspnoea VAS was 31.8; the mean Yung ASS was 4.95	SMD 0.01 higher (0.11 lower to 0.12 higher)	-	1130 (2 RCTs)	⊕⊕◯◯ LOW [26]	1 study reported Yung ASS and the other change in dyspnoea VAS

Admission at first presentation	819 per 1000	778 per 1000 (745 to 819)	RR 0.95 (0.91 to 1.00)	1308 (4 RCTs)	⊕⊕⊕◯ MODERATE [789]	Adults vs children test for subgroup difference: P = 0.72, I^2 = 0%
Readmission (7 to 30 days)	26 per 1000	46 per 1000 (22 to 100)	RR 1.80 (0.84 to 3.87)	750 (2 RCTs)	⊕⊕◯◯ LOW [10]	Outcome measured at 7 days in 1 study and 30 days in the other
Serious adverse events (during admission)	43 per 1000	Not estimable. See comment.	-	557 (2 RCTs)	⊕⊕⊕◯ MODERATE [11]	Risk difference: −0.03 (95% CI −0.06 to 0.00) Adults vs children test for subgroup difference: P = 0.39, I^2 = 0% Goodacre 2013 also reported participants with 1 or more SAE within 30 days: 35/332 in the $MgSO_4$ group and 28/358 in the placebo group (RD: 0.03; 95% CI −0.02 to 0.07)
Any adverse event (during admission)	144 per 1000	Not estimable. See comment.	-	1197 (2 RCTs)	⊕⊕⊕⊕ HIGH	Risk Difference: 0.01 (95% CI −0.03 to 0.05) Adults vs children test for subgroup difference: P = 0.34, I^2 = 0% Goodacre 2013 also reported participants with 1 or more adverse event within 30 days: 52/332 in the $MgSO_4$ group and 36/358 in the placebo group (OR 1.66, 95% CI 1.05 to 2.62)

GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION

Updated 2018

Adolescent and children 6-11 year old



Adolescent and children 6-11 year old

Magnesium

Intravenous magnesium sulfate is not recommended for routine use in asthma exacerbations; however, when administered as a single 2 g infusion over 20 minutes, it reduces hospital admissions in some patients, including adults with FEV_1 <25–30% predicted at presentation; adults and children who fail to respond to initial treatment and have persistent hypoxemia; and children whose FEV_1 fails to reach 60% predicted after 1 hour of care[426-428] (Evidence A). Randomized, controlled trials that excluded patients with more severe asthma showed no benefit with the addition of intravenous or nebulized magnesium compared with placebo in the routine care of asthma exacerbations in adults and adolescents[429,430] or children.[430,431] Nebulized salbutamol is most often administered in normal saline; however, it can also be administered in isotonic magnesium sulfate. While the overall efficacy of this practice is unclear, pooled data from three trials suggest possible improved pulmonary function in those with severe asthma exacerbations (FEV_1 <50% predicted)[432] (Evidence B).

Children < 5 years old

Box 6-11.Initial management of asthma exacerbations in children 5 years and younger

Therapy	Dose and administration
Supplemental oxygen	24% delivered by face mask (usually 1 L/minute) to maintain oxygen saturation 94–98%
Short-acting beta$_2$-agonist (SABA)	2–6 puffs of salbutamol by spacer, or 2.5 mg of salbutamol by nebulizer, every 20 minutes for first hour*, then reassess severity. If symptoms persist or recur, give an additional 2–3 puffs per hour. Admit to hospital if >10 puffs required in 3–4 hours.
Systemic corticosteroids	Give initial dose of oral prednisolone (1–2 mg/kg up to a maximum 20 mg for children <2 years old; 30 mg for children 2–5 years) OR, intravenous methylprednisolone 1 mg/kg 6-hourly on day 1
Additional options in the first hour of treatment	
Ipratropium bromide	For children with moderate-severe exacerbations, 2 puffs of ipratropium bromide 80mcg (or 250mcg by nebulizer) every 20 minutes for 1 hour only
Magnesium sulfate	Consider nebulized isotonic magnesium sulfate (150mg) 3 doses in the first hour of treatment for children aged ≥2 years with severe exacerbation (Box 6-9, p.118)

*If inhalation is not possible an intravenous bolus of terbutaline 2 mcg/kg may be given over 5 minutes, followed by continuous infusion of 5 mcg/kg/hour[541] (Evidence C). The child should be closely monitored, and the dose should be adjusted according to clinical improvement and side-effects. See below for additional and ongoing treatment, including controller therapy.

Children < 5 years old

Magnesium sulfate

The role of magnesium sulfate is not yet established for children 5 years and younger, because there are few studies in this age group. Nebulized isotonic magnesium sulfate may be considered as an adjuvant to standard treatment with nebulized salbutamol and ipratropium in the first hour of treatment for children ≥2 years old with acute severe asthma (e.g. oxygen saturation <92%, Box 6-9, p.118), particularly those with symptoms lasting <6 hours.[540] Intravenous magnesium sulfate in a single dose of 40-50 mg/kg (maximum 2 g) by slow infusion (20–60 minutes) has also been used.

III. CONCLUSION

- Nebulized isotonic $MgSO_4$ = Bronchodilator.
- Management =worsening /exacerbations asthma.
- Corchrane 2005-2012-2017+ GINA 2018
  1. Nebulized isotonic $MgSO_4$ + Salbutamol + Ipratropium
  2. Nebulized isotonic $MgSO_4$ + Salbutamol
  3. Nebulized isotonic $MgSO_4$
- Safety , few of side effects.


Thank You
For Your Attention!