

Table S1: Details of search strategy

Search strategy for PubMed database (from its inception to June, 2019)		
No.	Search strategy	Items found
#1	((((((((("hypertone"[All Fields] OR "hypertonic"[All Fields]) OR "hypertonics"[All Fields]) OR "muscle hypertonia"[MeSH Terms]) OR ("muscle"[All Fields] AND "hypertonia"[All Fields])) OR "muscle hypertonia"[All Fields]) OR "hypertonicity"[All Fields]) OR ("high"[All Fields] AND (((("osmosis"[MeSH Terms] OR "osmosis"[All Fields]) OR "osmotic"[All Fields]) OR "osmotical"[All Fields]) OR "osmotically"[All Fields]) OR "osmotics"[All Fields]))) OR 3[UID]) OR 5[UID]) OR 7[UID]	45390
#2	((((("saline solution"[MeSH Terms] OR ("saline"[All Fields] AND "solution"[All Fields])) OR "saline solution"[All Fields]) OR "saline"[All Fields]) OR "salines"[All Fields]) OR (((((((("pharmaceutical solutions"[Pharmacological Action] OR "solutions"[MeSH Terms]) OR "solutions"[All Fields]) OR "solution"[All Fields]) OR "pharmaceutical solutions"[MeSH Terms]) OR ("pharmaceutical"[All Fields] AND "solutions"[All Fields])) OR "pharmaceutical solutions"[All Fields]) OR "solotal"[All Fields]) OR "solute"[All Fields]) OR "solute s"[All Fields]) OR "soluted"[All Fields]) OR "solute s"[All Fields]) OR ("solution s"[All Fields]) OR ((("sodium chloride"[MeSH Terms] OR ("sodium"[All Fields] AND "chloride"[All Fields])) OR "sodium chloride"[All Fields])	965,26 6
#3	((((((((("cystic fibrosis"[MeSH Terms] OR ("cystic"[All Fields] AND "fibrosis"[All Fields])) OR "cystic fibrosis"[All Fields]) OR (((("cerebrospinal fluid"[MeSH Subheading] OR ("cerebrospinal"[All Fields] AND "fluid"[All Fields])) OR "cerebrospinal fluid"[All Fields]) OR "cf"[All Fields])) OR (((("cystic fibrosis"[MeSH Terms] OR ("cystic"[All Fields] AND "fibrosis"[All Fields])) OR "cystic fibrosis"[All Fields]) OR "mucoviscidosis"[All Fields])) OR (((("pulmonary disease, chronic obstructive"[MeSH Terms] OR ((("pulmonary"[All Fields] AND "disease"[All Fields]) AND "chronic"[All Fields]) AND "obstructive"[All Fields])) OR "chronic obstructive pulmonary disease"[All Fields]) OR "copd"[All Fields])) OR (((("pulmonary disease, chronic obstructive"[MeSH Terms] OR ((("pulmonary"[All Fields] AND "disease"[All Fields]) AND "chronic"[All Fields]) AND "obstructive"[All Fields])) OR "chronic obstructive pulmonary disease"[All Fields]) OR (((("chronic"[All Fields] AND "obstructive"[All Fields]) AND "pulmonary"[All Fields]) AND "disease"[All Fields])) OR (((("pulmonary disease, chronic obstructive"[MeSH Terms] OR ((("pulmonary"[All Fields] AND "disease"[All Fields]) AND "chronic"[All Fields]) AND "obstructive"[All Fields])) OR "chronic obstructive pulmonary disease"[All Fields]) OR (((("chronic"[All Fields] AND "obstructive"[All Fields]) AND "lung"[All Fields]) AND "disease"[All Fields])) OR "chronic obstructive lung disease"[All Fields])) OR (((("pulmonary disease, chronic obstructive"[MeSH Terms] OR ((("pulmonary"[All Fields] AND "disease"[All Fields]) AND "chronic"[All Fields]) AND "obstructive"[All Fields])) OR "chronic obstructive pulmonary disease"[All Fields]) OR (((("chronic"[All Fields] AND "obstructive"[All Fields]) AND "airway"[All Fields]) AND "disease"[All Fields])) OR "chronic obstructive airway disease"[All Fields])) OR (((("bronchiectasies"[All Fields] OR "bronchiectasis"[MeSH Terms]) OR "bronchiectasis"[All Fields]) OR "bronchiectases"[All Fields])) OR (((("ciliary motility disorders"[MeSH Terms] OR ("ciliary"[All Fields] AND "motility"[All Fields]) AND "disorders"[All Fields])) OR "ciliary motility disorders"[All Fields]) OR ((("primary"[All Fields] AND "ciliary"[All Fields]) AND "dyskinesia"[All Fields])) OR "primary ciliary dyskinesia"[All Fields])) OR ("prev chronic dis"[Journal] OR "pcd"[All Fields])) OR ("muco-obstructive"[All Fields] AND (((("disease"[MeSH Terms] OR "disease"[All Fields]) OR "diseases"[All Fields]) OR "disease s"[All Fields]) OR "diseased"[All Fields])) OR ("muco-obstructive"[All Fields] AND ((("lung diseases"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields])) OR "lung diseases"[All Fields]))	291686
#4	#1 AND #2 AND #3	786
Search strategy for EMBASE database (from its inception to June, 2019)		
No.	Search strategy	Items found

#1	hypertonic OR high osmotic OR 3% OR 5% OR 7%	326470
		64
#2	saline OR solution OR Sodium Chloride	100264
		8
#3	cystic fibrosis OR CF OR mucoviscidosis OR COPD OR chronic obstructive pulmonary disease OR chronic obstructive lung disease OR chronic obstructive airway disease OR bronchiectasis OR muco-obstructive diseases OR muco-obstructive lung diseases	299656
#4	#1 AND #2 AND #3	9674

Search strategy for CENTRAL database (from its inception to June, 2019)

No.	Search strategy	Items found
#1	hypertonic OR high osmotic OR 3% OR 5% OR 7%	113612
		9
#2	saline OR solution OR Sodium Chloride	64042
	cystic fibrosis OR CF OR mucoviscidosis OR COPD OR chronic obstructive pulmonary disease OR chronic	
#3	obstructive lung disease OR chronic obstructive airway disease OR bronchiectasis OR muco-obstructive diseases OR muco-obstructive lung diseases	33078
#4	#1 AND #2 AND #3	1505

Table S2: relevant ongoing studies in the international trial registers

ClinicalTrials.gov	
NCT02378467	CF
NCT00753987	CF
NCT01094704	CF
NCT01792271	COPD
NCT02950883	CF
NCT01377792	CF
NCT01031706	CF
NCT02266875	COPD
ISRCTN Registry	
ISRCTN89040295	CF
ISRCTN13083896	CF

Table S3: Characteristic of included studies

Study	Location	Study design	Age (years)	Sample size	Intervention	Control	Method	Outcomes
Amin 2010	Canada (2008)	Randomized controlled cross-over study	6-18	19	HS(7%)+ salbutamol	NS(0.9%)+ salbutamol	2/day*4 weeks	LCI, FEV1, FVC, FEF25-75, QOL (CFQ-R)
Amin 2016	Canada (2012-2014)	Randomized controlled cross-over study	14.0 (7, 56)#	18	HS(7%)+ salbutamol	NS(0.9%)+ salbutamol	5/day*2 weeks	LCI, FEV1, FEF25-75
Dentice 2016	Australia (2005-2013)	RCT	Con 27±9, 7%HS 28±9	132	HS(7%)	0.12% saline	3/day during hospitalization	FEV1, FVC, QOL (SF36, CFQ)
Cystic fibrosis Elkins 2006	Australia (2000-2003)	RCT	18.4 ±9.3	164	HS(7%)+ quinine sulfate	NS(0.9%)+ quinine sulfate	2/day*48 weeks	FEV1, FVC, FEF25-75, QOL (SF36, CFQ), PE, AE
Eng 1996	Australia (2008)	RCT	Con 16.7 (8, 36), HS 16.1 (7, 25)# 3%HS 10.6 ±2.87, 7%HS 10.87 ±3.64	52	HS(6%)	NS(0.9%)	2/day*2 weeks	FEV1, FVC, QOL (VAS), AE
Gupta 2012	India	RCT	10.5 (8.9 - 12.4) &	30	HS(7%)	HS(3%)	2/day*28 days	FEV1, FVC, PEFR, QOL (VAS)
Laube 2011	US	Randomized controlled	10.5 (8.9 - 12.4) &	12	HS(7%)+ salbutamol	saline(0.12%) + salbutamol	1/2weeks, 3 times in total	MCC

		cross-over study							
Mainz 2016	Germany (2010-2013)	Randomized controlled cross-over study	22.8 ± 12	64	HS(6%)	NS(0.9%)	1/day*28 days.	FEV1	
Nenna 2017	Italy (2012-2013)	Randomized controlled cross-over study	5.7 ± 0.8	12	HS(7%)	NS(0.9%)	2/day*16 weeks	FEV1, FVC, FEF25-75,	
Riedler 1996	Australia	Randomized controlled cross-over study	16.5 (13-20)#	10	HS(6%)	NS(0.9%)	1/day*1 time	FEV1, QOL (VSA)	
Robinson 1996	Australia	Randomized controlled cross-over study	21.9 (18-28)#	12	HS(7%)	NS(0.9%)	1/day*1 time	MCC, FEV1	
Robinson 1997	Australia	Randomized controlled cross-over study	22.1 ± 3.8	10	HS(12%),HS(7%),HS(3%)	NS(0.9%)	1/day*1 time	MCC, FEV1	
Rosenfeld 2012	USA and Canada (2009-2011)	RCT	Con 2.3 ± 1.5, HS 2.2 ± 1.4	321	HS(7%)+ albuterol or levalbuterol	NS(0.9%)+ albuterol or levalbuterol	2/day*48 weeks	FEV0.5, FEF25-75, QOL(CFQ), PE, AE	
Stahl 2018	Germany (2012-2015)	RCT	0.26 ± 0.08	40	HS(6%)	NS(0.9%)	2/day*12 months	LCI	

Non-Cystic fibrosis Bronchiectasis	Kellett 2005	UK	Randomized controlled cross-over study	Females 55±3.6, Males 64±3.8	23	HS(7%)+terbutaline	NS(0.9%)+terbutaline	1/week*4 week	Ease of expectoration (VAS), FEV1, FVC
	Kellett 2011	UK	Randomized controlled cross-over study	56.6±14.6	28	HS(7%)	NS (0.9%)	1/day*3 months	FEV1, FVC, QOL(St George), ease of expectoration (VAS)
	Nicolson 2012	Australia (2008-2009)	RCT	Con 56±15, HS 58±15	40	HS (6%)	NS (0.9%)	2/day*12 months	Ease of expectoration (VAS), FEV1, FEF25-75%
	Herrero-Cortina 2018	Spain (2015)	Randomized controlled cross-over study	64.0±17.5 months	28	HS (7%)	NS (0.9%)	1/day*4 times	Sputum expectoration, FEV1, FVC, AE
COPD	Clarke 1979	US	Randomized controlled cross-over study	62.8±8.0	22	HS (7.1%)	NS (0.9%)	2/day*3 days	Lung clearance, lung function
	Valderramas 2009	Brasil (2004-2006)	RCT	Con 67±6.5; 3%HS 68±6.5	68	HS(3%)+salbutamol	NS(0.9%)+salbutamol	3/week*8 weeks	QOL, AE
PCD	Tamara 2017	Netherlands (2014-2015)	Randomized controlled cross-over study	47.6 (26.9-58.1) #	22	HS(7%)	NS(0.9%)	2/day*12 weeks	QOL(SGRQ, QOL-B), ease of expector

ation
(VAS)

HS: hypertonic saline, NS: normal saline, RCT: Randomized controlled study, PCD: primary ciliary dyskinesia, COPD: chronic obstructive pulmonary disease, AE: adverse event, MCC: mucociliary clearance, LCI: lung clearance index, RDAI: Respiratory Distress Assessment Instrument, FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, PEF: peak expiratory flow, QOL: quality of life, VSA: visual analogue score, SGRQ: St George's Respiratory Questionnaire, ED: emergency department, *: median (25th, 75th), #: median (range), &: median (IQR). 2/day*12 weeks: Twice daily inhalations for 12 weeks.