Appendix 1. Search strategies

Embase

(postoperative complication/ or perioperative period/ or peroperative care/ or preoperative

care/ or postoperative care/ or anesthesia/ or intra*operative complication*.mp or

post*operative complication*.mp or peri*operative complication*.mp or pre*operative

care.mp or intra*operative care.mp or peri*operative care.mp or post*operative care.mp or

an*esthesia.mp)

Combined with the AND Boolean operator for the following descriptive terms relevant to

post-operative respiratory complications and based on the EPCO definitions:

(pneumonia/ or respiratory tract infection/ or lung infection/ or respiratory failure/ or

atelectasis/ or pleural effusion/ or pneumonia.mp or respiratory infection.mp or pulmonary

infection.mp or respiratory failure.mp or atelectasis.mp or pleural effusion.mp or respiratory

complication*.mp)

Limits

Human studies only

Year of publication: 1990 to December 12 2017

Randomized controlled trial

MEDLINE

(Postoperative complications/ or Intraoperative care/ or Postoperative care/ or Perioperative

care/ or Preoperative care/ or Intraoperative complications/ or Anesthesia/ or intra*operative

complication*.mp or post*operative complication*.mp or peri*operative complication*.mp

or pre*operative care.mp or intra*operative care.mp or peri*operative care.mp or

post*operative care.mp or an*esthesia.mp)

Combined with the AND Boolean operator for the following descriptive terms relevant to

post operative respiratory complications and based on the EPCO definitions:

(Respiratory tract infections/ or Respiratory insufficiency/ or Pneumonia/ or Pulmonary

atelectasis/ or Pleural effusion/ or pneumonia.mp or respiratory infection.mp or pulmonary

infection.mp or respiratory failure.mp or atelectasis.mp or pleural effusion.mp or respiratory

complication*.mp)

Limits

Human studies only

Year of publication: 1990 to December 12 2017

Randomised controlled trial

CINHAL

(intra*operative complication* or post*operative complication* or peri*operative

complication* or pre*operative care or intra*operative care or peri*operative care or

post*operative care or an*esthesia)

Combined with the AND Boolean operator for the following descriptive terms relevant to

post operative respiratory complications and based on the EPCO definitions:

(pneumonia or respiratory infection or pulmonary infection or respiratory failure or

atelectasis or pleural effusion or respiratory complication*)

Limits

Year of publication: 1990 to December 12 2017

Randomised controlled trial

CENTRAL

(intra*operative complication* or post*operative complication* or peri*operative

complication* or pre*operative care or intra*operative care or peri*operative care or post*operative care or an*esthesia)

Combined with the AND Boolean operator for the following descriptive terms relevant to post operative respiratory complications and based on the EPCO definitions:

(pneumonia or respiratory infection or pulmonary infection or respiratory failure or atelectasis or pleural effusion or respiratory complication*)

Limits

Year of publication: 1990 to December 12 2017

Trials

Inclusion/exclusion criteria

The inclusion criteria are:

- Studies of patients aged 18 or over
- Studies of patients undergoing elective and emergency non-cardiac surgery
- Studies published with primary data in full peer reviewed journals

The following will be excluded from the review:

- Studies of patients under the age of 18
- Studies of patients undergoing cardiac surgery
- Studies published before 1990
- Studies lacking explicitly defined criteria or definitions for PPCs
- Studies of organ transplantation surgery, due to the effects of immunosuppressive drugs on the likelihood of developing PPCs

- Studies of only physiological (e.g. lung volumes and flow measurements) or only biochemical (e.g. lung inflammatory markers) parameters, rather than clinical outcomes measures
- Studies where the intervention is directly related to surgical technique

Citation searching of reference lists

In addition, the clinical trials identified in the primary search were then snowballed by hand searching of references lists and searching for citations on Web of Science.

Appendix 2. Characteristics of studies and meta-analysis of trials according to intervention group

1. Incentive spirometry

Study Author and Year	Study Sample and Country	Intervention description	Timing of Intervention Delivery	Pulmonary Outcomes	Risk of bias
Agostini 2013	n=180, UK, single centre	Post-operative supervised use of incentive spirometry once or twice daily until hospital discharge	Post-operative	Composite PPC	Some concerns
Gosselink 2000	n=67, Belgium, single centre	Post-operative supervised use of incentive spirometry with target volume set daily by a physiotherapist	Post-operative	Composite PPC	High risk
Hall 1991	n=876, Australia, single centre	Prophylactic use of incentive spirometry for at least 5 mins in every waking hour, when possible started before surgery	Pre-operative and post-operative	Composite PPC, respiratory failure	High risk
Hall 1996	n=63, Australia, single centre	Prophylactic use of incentive spirometry pre and post surgery	Pre-operative and post-operative	Composite PPC, respiratory infection, respiratory failure, atelectasis	High risk
Lunardi 2015	n=137, Brazil, single centre	Post-operative use of 2 different types of incentive spirometry and deep breathing exercises for 5 days	Post-operative	Composite PPC	High risk
Pantel 2017	n=224, USA, single centre	Postoperative supervised use of incentive spirometry In addition, preoperative teaching and postoperative coaching and prompting.	Post-operative	Composite PPC, respiratory infection, respiratory failure, atelectasis	High risk

	Experimental		Control		Risk Ratio			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Hall 1991	68	431	68	445	54.4%	1.03 [0.76, 1.41]	1991	+
Hall 1996	35	231	28	225	24.3%	1.22 [0.77, 1.93]	1996	
Gosselink 2000	4	32	4	35	3.1%	1.09 [0.30, 4.01]	2000	
Agostini 2013	11	92	13	88	9.3%	0.81 [0.38, 1.71]	2013	
Lunardi 2015	6	67	8	70	5.1%	0.78 [0.29, 2.14]	2015	
Pantel 2017	8	112	4	112	3.8%	2.00 [0.62, 6.45]	2017	+
Total (95% CI)		965		975	100.0%	1.06 [0.85, 1.34]		•
Total events	132		125					
Heterogeneity: Tau2 =	Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.35$, $df = 5$ (P = 0)					0%		0.01 0.1 1 10 100
Test for overall effect	Test for overall effect: $Z = 0.53$ ($P = 0.59$)							Favours [experimental] Favours [control]

Figure 1.1 Forest plot comparing proportions of patient developing PPCs in RCTs of prophylactic incentive spirometry compared with standard medical care.

	Experimental		Control		Risk Ratio			Risk Ratio
Study or Subgroup	Events Total		Events	Events Total Weight M-		M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Hall 1996	4	231	0	225	54.5%	8.77 [0.47, 161.91]	1996	
Pantel 2017	1	112	0	112	45.5%	3.00 [0.12, 72.86]	2017	
Total (95% CI)		343		337	100.0%	5.38 [0.63, 46.30]		
Total events	5		0					
Heterogeneity: Tau ² = Test for overall effect				(P = 0	.62); I ² =	0%		0.01 0.1 1 10 100 Favours [experimental] Favours [control]

Figure 1.2 Forest plot comparing proportions of patient developing respiratory infections in RCTs of prophylactic incentive spirometry compared with standard medical care.

	Experimental			Control			Mean Difference			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	r IV, Random, 95% CI
Hall 1991	7.7	5.15	431	7.3	5.2	445	30.9%	0.40 [-0.29, 1.09]	1991	
Hall 1996	9	4.48	231	10	5.22	225	28.1%	-1.00 [-1.89, -0.11]	1996	•
Gosselink 2000	14	8	32	15	7	35	6.4%	-1.00 [-4.61, 2.61]	2000	+
Agostini 2013	6	1.51	92	5	0.75	82	34.5%	1.00 [0.65, 1.35]	2013	•
Total (95% CI)			786				100.0%			
Heterogeneity: $Tau^2=0.74$; $Chi^2=18.26$, $df=3$ (P = 0.0004); Test for overall effect: Z = 0.24 (P = 0.81)										-100 -50 0 50 100 Favours [experimental] Favours [control]

Figure 1.3 Forest plot comparing hospital length of stay (days) in RCTs of prophylactic incentive spirometry compared with standard medical care.

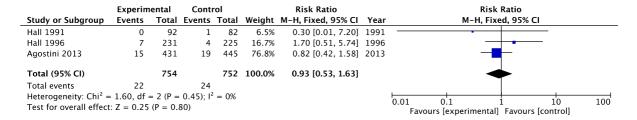


Figure 1.4 Forest plot comparing mortality in RCTs of prophylactic incentive spirometry compared with standard medical care.

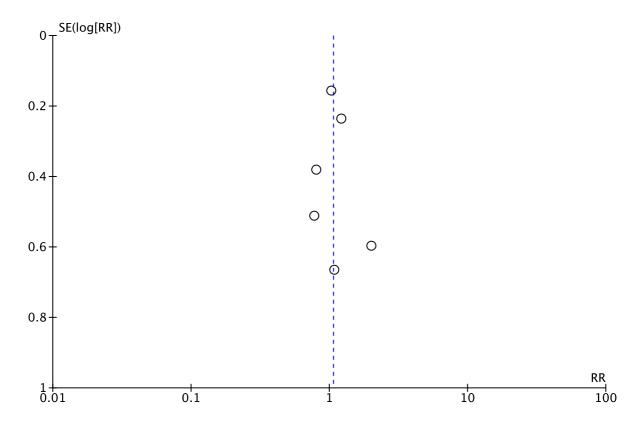


Figure 1.5 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of incentive spirometry.

2. Supervised physiotherapy

Study Author and Year	Study Sample and Country	Intervention description	Timing of Intervention Delivery	Pulmonary Outcomes	Risk of bias
Brocki, 2016	n=69, Denmark, single centre	Preoperative and postoperative supervised chest physiotherapy including at home post discharge for up to two weeks	Pre-operative and post-operative	Composite PPC, respiratory infection, respiratory failure, atelectasis	High risk
Chumillas, 1998	n=81, Spain, single centre	Supervised chest physiotherapy pre- operatively and until discharge, with early post-operative ambulation	Pre-operative and post-operative	Composite PPC	High risk
Condie, 1993	n=310, European, multi-centre	Postoperative supervised respiratory physiotherapy and early postoperative ambulation	Pre-operative and post-operative	Respiratory infection	High risk
Dronkers, 2008	n=20, Netherlands, single centre	Preoperative respiratory inspiratory muscle training	Pre-operative	Atelectasis	Some concerns
Kulkarni, 2010	n=49, UK, single centre	Supervised preoperative repiratory physiotherapy	Pre-operative	Respiratory infection	High risk
Ludwig	n=135, Germany, single centre	Postoperative respiratory physiotherapy from postoperative day one until discahrge	Post-operative	Composite PPC, respiratory infection	High risk
Mackay 2005	n=50, Australia, single centre	Postoperative respiratory physiotherapy	Post-operative	Composite PPC	High risk

Olsen 1997	n=364, Sweden, single centre	Pre-operative education and postoperative supervised respiratory physiotherapy	Pre-operative and post-operative	Composite PPC, respiratory infection	High risk
Olsen 1999	n=80, Sweden, single centre	Preoperative education and postoperative supervised respiratory physiotherapy until discharge	Pre-operative and post-operative	Respiratory infection, respiratory failure	High risk
Reeve 2010	n=76, New Zealand, single centre	Supervised and non-supervised postoperative respiratory physiotherapy. Exercises continued at home post-discharge	Post-operative	Composite PPC	High risk
Silva 2013	n=56, Australia, single cente	Postoperative supervised respiratory physiotherapy and early ambulation	Post-operative	Composite PPC	Low risk
Van Adrichem 2014	n=39, Netherlands, single centre	preoperative respiratory high intensity muscle training	Pre-operative	Composite PPC, respiratory infection	High risk

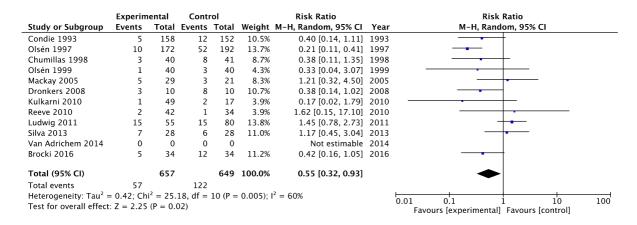


Figure 2.1 Forest plot comparing proportions of patients developing PPCs in RCTs of prophylactic supervised respiratory physiotherapy compared with standard medical care. Van Adrichem 2014 was not included in the meta-analysis because there was no standard medical care group.

	Experim	ental	Cont	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events Total		Events Total		Weight M-H, Random, 95% CI Ye		Year	M-H, Random, 95% CI
Condie 1993	5	158	12	152	40.0%	0.40 [0.14, 1.11]	1993	
Olsén 1997	1	172	13	192	10.1%	0.09 [0.01, 0.65]	1997	
Olsén 1999	0	40	1	40	4.1%	0.33 [0.01, 7.95]	1999	•
Kulkarni 2010	1	49	2	17	7.6%	0.17 [0.02, 1.79]	2010	
Ludwig 2011	3	55	4	80	19.6%	1.09 [0.25, 4.68]	2011	
Van Adrichem 2014	0	0	0	0		Not estimable	2014	
Brocki 2016	2	34	7	34	18.5%	0.29 [0.06, 1.28]	2016	
Total (95% CI)		508		515	100.0%	0.36 [0.19, 0.69]		•
Total events	12		39					·
Heterogeneity: Tau ² =	Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.83$, $df = 5$ (P =			(P = 0)	.44); $I^2 =$	0%		
Test for overall effect: $Z = 3.07 (P = 0.002)$								6.01 0.1 1 10 100 Favours [experimental] Favours [control]

Figure 2.2 Forest plot comparing proportions of patient developing respiratory infections in RCTs of prophylactic supervised respiratory physiotherapy compared with standard medical care. Van Adrichem 2014 was not included in the meta-analysis because there was no standard medical care group.

	Experimental			C	ontrol			Mean Difference		Mean Differe	ence	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 9	5% CI	
Christensen 1991	21.4	28.6	34	13.4	16.98	17	1.5%	8.00 [-4.55, 20.55]	1991	+-	_	
Olsén 1997	8.8	4.5	172	9	5.1	192	46.3%	-0.20 [-1.19, 0.79]	1997	•		
Mackay 2005	10.4	3	29	13.3	4.5	21	26.8%	-2.90 [-5.11, -0.69]	2005	=		
Ludwig 2011	18.4	23.6	55	19.1	26.42	80	3.2%	-0.70 [-9.21, 7.81]	2011	+		
Van Adrichem 2014	0	0	0	0	0	0		Not estimable	2014			
Brocki 2016	8.1	5.1	34	8.4	5.9	34	22.1%	-0.30 [-2.92, 2.32]	2016	†		
Total (95% CI)			324			344	100.0%	-0.84 [-2.41, 0.74]		•		
Heterogeneity: $Tau^2 = 1.15$; $Chi^2 = 6.63$, $df = 4$ (P = 0.16); $I^2 = 4$							40%			-100 -50 0	50	100
Test for overall effect	z = 1.0)4 (P =	= 0.30)							Favours [experimental] Favo		100

Figure 2.3 Forest plot comparing hospital length of stay (days) in RCTs of prophylactic supervised respiratory physiotherapy compared with standard medical care.

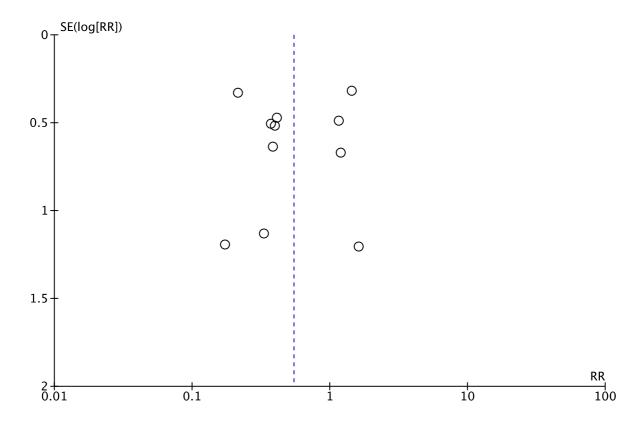


Figure 2.4 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of incentive spirometry.

3. Drug therapies to improve pulmonary function

Study Author	Study Sample and		Timing of Intervention	Pulmonary	D. 1
and Year	Country	Intervention description	Delivery	Outcomes	Risk of bias
Dilworth 1994	n=43, UK single, centre	5mg nebulised Salbutamol from 1hour preoperatively, then at 6 h intervals for 2 days postoperatively	Pre-operative and post-operative (beta blocker)	Composite PPC	High risk
Fegiz 1991	n=252, Italy, multi-centre	1000mg Ambroxol administered intravenously for 3 days before surgery, on the day of surgery and 2 days after surgery	Pre-operative and post-operative (secretolytic)	Respiratory infection	High risk

Gao 2014	n=60, China, single centre	1000mg Ambroxol administered intravenously on the day of surgery and for four days after surgery	Pre-operative and post-operative (secretolytic)	Composite PPC, respiratory infection, atelectasis	High risk
Li 2014	n=40, China, single centre	Img Budesonide nebulised twice daily from postoperative day one to day three after surgery	Post-operative (inhaled steroid)	Composite PPC, respiratory infection	High risk
Ong 2004	n=73, New Zealand, single centre	1200mg Co-amoxiclav administered intravenously for five days postoperatively	Post-operative (prophylactic antibiotics)	Composite PPC, respiratory infection, atelectasis	Low risk
Perkins 2014	n=362, UK, multi- centre	100mcg Salmeterol inhaled by spacer device 2 hours before surgery and every 12 hours for 72 hours after surgery	Pre-operative and post-operative (inhaled beta agonist)	Respiratory infection, respiratory failure	Low risk
Refai	n=140, Italy,	1000mg Ambroxol administered intravenously on the day of surgery and for	Pre-operative and post-operative	Composite PPC, respiratory infection, respiratory failure,	Some
2009	single centre	three days after surgery MgSO4 50 mg/kg administered	(secretolytic)	atelectasis Respratory	concerns
Sohn 2017	n=62, South Korea, single centre	intravenously fover 10 minutes, followed by a continuous infusion of 15 mg/kg/h during surgery	Intra-operative (magnesium sulphate)	infection, pulmonary effusion	Low risk

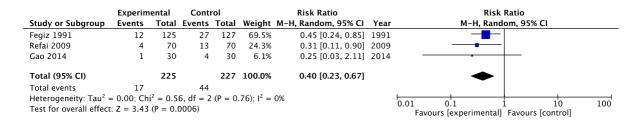


Figure 3.1 Forest plot comparing proportions of patients developing PPCs in RCTs of prophylactic mucolytic (Ambroxol) with placebo.

	Experimental		Control		Risk Ratio			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Fegiz 1991	1	125	4	127	25.8%	0.25 [0.03, 2.24]	1991	
Refai 2009	2	70	5	70	47.4%	0.40 [0.08, 1.99]	2009	
Gao 2014	1	30	4	30	26.9%	0.25 [0.03, 2.11]	2014	
Total (95% CI)		225		227	100.0%	0.31 [0.10, 0.95]		
Total events	4		13					
Heterogeneity: $Tau^2=0.00$; $Chi^2=0.17$, $df=2$ $(P=0.92)$; I^2 Test for overall effect: $Z=2.06$ $(P=0.04)$.92); I ² = (0%		0.01 0.1 1 10 100 Favours [experimental] Favours [control]

Figure 3.2 Forest plot comparing proportions of patients developing respiratory infection in RCTs of prophylactic mucolytic (Ambroxol) with placebo.

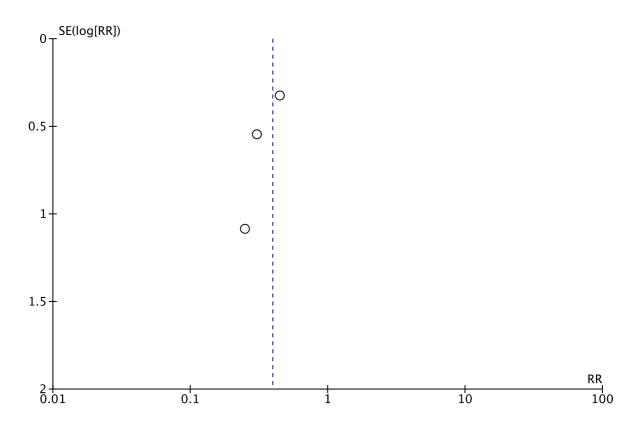


Figure 3.3 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of prophylactic mucolytic (Ambroxol).

	Experimental Control				Risk Ratio	Risk Ratio		
Study or Subgroup	Events Total		Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
Dilworth 1994	8	21	10	22	21.5%	0.84 [0.41, 1.71]		
Perkins 2014	41	179	44	183	78.5%	0.95 [0.66, 1.38]	#	
Total (95% CI)		200		205	100.0%	0.93 [0.67, 1.29]	•	
Total events	49		54					
Heterogeneity: Tau2 =	0.00; Ch	$i^2 = 0.1$	0, df = 1	(P = 0)	$.75$); $I^2 =$	0%	0.01 0.1 1 10 100	1
Test for overall effect: $Z = 0.45$ (P = 0.65)							0.01 0.1 1 10 100 Favours [experimental] Favours [control]	

Figure 3.4 Forest plot comparing proportions of patients developing respiratory infection in RCTs of inhaled beta agonists with placebo.

4. Intraoperative anaesthetic gas composition

Study Author and Year	Study Sample and Country	Intervention description	Timing of Intervention Delivery	Pulmonary Outcomes	Risk of bias
Akca 1999	n=30, Austria single centre	80% FiO2 during and for two hours following surgery	Intra-operative and post-operative	Atelectasis	Low risk
Meyhoff 2009	n=1386, Denmark, multi- centre	80% FiO2 during and for two hours following surgery	Intra-operative and post-operative	Respiratory infection, respiratory failure, atelectasis	Low risk
Myles 2007	n=2012, multi- national, multi- centre	Anaesthesia with a nitrous oxide-free gas mixture (80% O2, 20% N2)	Intra-operative	Composite PPC, respiratory infection,	Low risk

				atelectasis	
				Respiratory infection,	
	n=166, Denmark,	Subgroup analysis of obese patients from the PROXI trial. 80% FiO2 during and for 2		respiratory failure,	
Stæhr 2011	multi-centre	hours following surgery	Intra-operative	atelectasis	Low risk

	80% F	02	30% F	iO2		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Acka 1999	7	16	5	14	14.6%	1.23 [0.50, 3.00]	1999	
Meyhoff 2009	54	685	50	701	85.4%	1.11 [0.76, 1.60]	2009	#
Total (95% CI)		701		715	100.0%	1.12 [0.80, 1.58]		•
Total events	61		55					
Heterogeneity: Tau2 =	= 0.00; Ch	$ni^2 = 0.$.04, df =	1 (P =	0.83); $I^2 =$	= 0%		
Test for overall effect	z = 0.66	S(P=0)	0.51)					6.01 0.1 1 10 100 Favours [experimental] Favours [control]

Figure 4.1. Forest plot comparing proportions of patients developing PPCs in RCTs of high (0.8) versus low (0.3) perioperative inspired oxygen fraction.

5. Intraoperative ventilation strategies

Study Author and	Study Sample and		Timing of		
Year	Country	Intervention description	Intervention Delivery	Pulmonary Outcomes	Risk of bias
		Tidal volume 8ml/kg, Zero			
		PEEP - then immediately after			
		induction pressure-control			
		mode was started and			
		inspiratory time was increased			
		to 50% (inspiratory: expiratory			
		ratio was set to 1:1). Peak			
		airway inspiratory pressure			
		(Ppeak) was initially set to 20			
		cmH2O for three breaths, then			
		PEEP was increased in four			
		steps from 0 to 5 cmH2O for			
		three breaths, from 5 to 10			
		cmH2O for five breaths, from			
		10 to 15 cmH2O for seven			
		breaths and from 15 to 20			
		cmH2O for 10 breaths while			
		Ppeak increased to 45 cmH2O			
		and was maintained for three			
		more breaths. Followingthe			
		recruitment manoever, volume			
		control was re-established			
		using Vt 6 mL/kg and step-			
		wise reductions in PEEP from			
	0.0	20 to 15 cmH2O for three			
	n=81, Greece, single	breaths, and then to 8 cmH2O			Some
Aretha 2017	centre	until the end of surgery.	Intra-operative	Respiratory infection	concerns
		Tidal volume of 6–8 mL/kg of			
		predicted body weight,			
		ventilatory rate of 10			
		breaths/min, FIO2 of 0.4, and			
		inspiratory:expiratory ratio of			
		1:2 in pressure control mode.			
		Lungs were recruited by			
		increasing the PEEP gradually,			
	51 C V	from 4 cmH2O (2 breaths) to 6		D : : f :-	
CI : 2017	n=51, S. Korea,	cmH2O (2 breaths), 8 cmH2O		Respiratory infection	TT: 1 : 1
Choi 2017	single centre	(2 breaths), and finally 16	Intra-operative	and atelectasis	High risk

	ı	1100 (101 - 1) 10 - 10	1	1	ı
		cmH2O (10 breaths). After 10 breaths with 16 cmH2O, PEEP			
		was decreased stepwise as			
		before.			
		Tidal volume of 6-8 mL/kg			
		(IBW), PEEP 6-8 cm H2O,			
		and recruitment manoeuvres			
		repeated every 30 minutes		Composite PPC,	
	n=400, Europe,	after tracheal intubation (30		respiratory infection	Some
Futier 2013	multicentre	cm H2O for 30 seconds)	Intra-operative	and atelectasis	concerns
	n=40, Netherlands,	Tidal volume 6 mls/kg and			
Goda Choi 2006	single centre	PEEP of 10cmH2O	Intra-operative	Composite PPC	High risk
	n=16, China, single				
Hongwei Cai 2007	centre	Tidal volume 6ml/kg	Intra-operative	Atelectasis	High risk
		High frequency percussive			
		ventilation. FiO2 1.0, 500			
		cycles per minute, mean			
		pulsatile pressure 5cmH20,			
	n=44, Italy, single	inspiratory time-10.5 and			
Lucangelo 2009	centre	expiratory time-1.5.	Intra-operative	Respiratory infection	High risk
				Composite PPC,	
Milanna Vac-	n=100 C Va	FiO2 0.5 tidal malumo 6 m1/1		respiratory failure,	
Mikyung Yang	n=100, S. Korea,	FiO2 0.5, tidal volume 6 ml/kg and PEEP 5	Intra operative	pleural effusion and pneumothorax	High wigh
2011	single centre		Intra-operative	1	High risk
		Tidal volume of 6 ml/kg with		Composite PPC,	_
D 1 2015	n=39, S. Korea,	positive end-expiratory	1.	respiratory infection	Some
Park 2016	single centre	pressure (PEEP) of 5 cmH2O,	Intra-operative	and atelectasis	concerns
		12cm H2O PEEP + RMs after			
		intubation at the start of			
		ventilation; before tracheal			
		extubation; after each			
		accidental disconnection from the ventilator. RMs were			
		performed as follows: peak inspiratory pressure limit was			
		set at 45 cmH2O; tidal volume			
		was set at 8 ml kg 1 predicted			
		body weight (PBW), respir-			
		atory rate at 6 to 8 breaths min			
		1 (or lowest respiratory rate			
		that the anaesthesia ventilator			
		allows), and PEEP was set at			
		12 cmH2O; inspiratory to			
		expiratory (I:E) ratio was set at			
		1:2; tidal volumes were			
		increased in steps of 4 ml kg 1			
		PBW until a plateau pressure			
		of 30 to 35cmH2O was			
		attained; three breaths were			
		administered with a plateau			
		pressure of 30 to 35cmH2O;			
		peak inspiratory pressure limit,		Commonity DDC	
	n=904	respiratory rate, I:E ratio, and		Composite PPC,	
PROVE Network	n=894, multinational,	tidal volume were reset to the settings preceding each		respiratory infection, pleural effusion and	
investigators 2014	multicentre	recruitment manoeuver.	Intra-operative	atelectasis	Low risk
rosugators 2014	municinic	recruitment manocuver.	тии орегануе		LOWIISK
	26.6. " :			Respiratory infection,	
O	n=26, Saudi Arabia,	Tidal volume 4mls/kg v 6	Tutus as di	respiratory failure and	TT:-1 · · ·
Qutub 2014	single centre	mls/kg	Intra-operative	atelectasis	High risk
		PEEP 30cmH2O and			
	n=20 Propil singl-	inpsiratory plateau pressure 45			
Pamiatian 2011	n=30, Brazil, single	cmH2O for 2 mins after	Intro operative	Composite DDC	High might
Remistico 2011	centre	pneumoperitoneum deflated	Intra-operative	Composite PPC	High risk
		Tidal volumes of 7ml/kg ideal			
		body weight, 10cm H2O positive end-expiratory			
		pressure, and recruitment		Composite PPC,	
	n=53, Italy, single	maneuvers (pro- tective		respiratory infection	
Severonini 2013			Intra-operative		High rick
Severgnini 2013	cente	ventilation strategy)	Intra-operative	and atelectasis	High risk

Shen 2013	n=101, China, single centre	Tidal volume 5mls/kg and peep 5cmH2O	Intra-operative	Composite PPC	High risk
Talab 2009	n=58, Saudi Arabia, single	Use of 5 and 10 cm H2O PEEP	Intra-operative	Composite PPC and atelectasis	High risk
Treschen 2012	n=101, Germany, single centre	low (6 ml/kg) tidal volumes	Intra-operative	Composite PPC, respiratory infection, respiratory failure and pneumothorax	Low risk
Treschen 2017	n=57, Germany, single centre	As per PROVILHO trial (PROVE et al 2014)	Intra-operative	Composite PPC, respiratory infection, pleural effusion, atelectasis and pneumothorax	Low risk
Weingarten 2010	n=40, USA, single centre	Recruitment manoeuvres, tidal volume 6 ml/kg predicted body weight, and 12 cm H2O PEEP	Intra-operative	Respiratory infection and atelectasis	High risk
Wetterslev 2001	n=40, Denmark, single centre	5-10cm H2O PEEP	Intraoperative	Respiratory infection and respiratory failure	Low risk

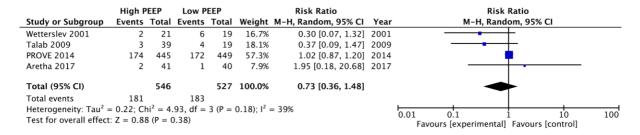


Figure 5.1. Forest plot comparing proportions of patients developing PPCs in RCTs of high PEEP (\geq 5cm H₂O) versus low PEEP (\leq 2cm H₂O) during intra-operative mechanical ventilation.

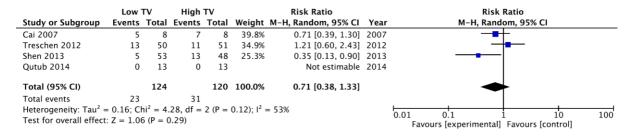


Figure 5.2. Forest plot comparing proportions of patients developing PPCs in RCTs of low tidal volume (≤ 6ml/kg predicted body weight) versus high tidal volume (≥ 8ml/kg) during intra-operative mechanical ventilation.

	Experim	ental	Conti	rol		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI	
Weingarten 2010	4	20	5	10	12.6%	0.40 [0.14, 1.17]	2010		
Yang 2011	2	50	11	50	8.8%	0.18 [0.04, 0.78]	2011		
Severgnini 2013	5	26	14	27	15.3%	0.37 [0.16, 0.88]	2013		
Futier 2013	35	200	72	200	23.0%	0.49 [0.34, 0.69]	2013	- 	
PROVE 2014	174	445	172	449	25.0%	1.02 [0.87, 1.20]	2014	+	
Choi 2017	3	26	8	25	11.1%	0.36 [0.11, 1.21]	2017		
Aretha 2017	2	41	1	40	4.3%	1.95 [0.18, 20.68]	2017	-	
Total (95% CI)		808		801	100.0%	0.52 [0.30, 0.88]		•	
Total events	225		283						
Heterogeneity: Tau2 =	= 0.29; Ch	$i^2 = 27.$	07, df =	6 (P =	0.0001);	$1^2 = 78\%$		0.01 0.1 1 10	100
Test for overall effect	Z = 2.43	(P = 0.	01)					Favours [experimental] Favours [control]	100

Figure 5.3. Forest plot comparing proportions of patients developing PPCs in RCTs of a lung protective ventilation strategy (PEEP \geq 5 cm H₂O + TV \leq 8ml/kg PBW + recruitment manoeuvres) versus no protective strategy during intra-operative mechanical ventilation.

	Experim	ental	Cont	rol		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M–H, Random, 95% CI	
Weingarten 2010	0	20	1	10	4.1%	0.17 [0.01, 3.94]	2010	•	
Severgnini 2013	5	26	14	27	22.6%	0.37 [0.16, 0.88]	2013		
Futier 2013	3	200	16	200	16.5%	0.19 [0.06, 0.63]	2013		
PROVE 2014	68	445	75	449	33.8%	0.91 [0.68, 1.24]	2014	+	
Choi 2017	0	26	1	25	4.0%	0.32 [0.01, 7.53]	2017	•	
Aretha 2017	7	41	5	40	19.0%	1.37 [0.47, 3.95]	2017		
Total (95% CI)		758		751	100.0%	0.56 [0.28, 1.09]		•	
Total events	83		112						
Heterogeneity: Tau ² =	= 0.32; Ch	$i^2 = 11.$	56, df =	5 (P =	0.04); I ² =	= 57%		0.01 0.1 1 10	100
Test for overall effect	:: Z = 1.72	(P = 0.	09)					Favours [experimental] Favours [control]	100

Figure 5.4. Forest plot comparing proportions of patients developing respiratory infection in RCTs of a lung protective ventilation strategy (PEEP \geq 5 cm H2O + TV \leq 8ml/kg PBW + recruitment manoeuvres) versus no protective strategy during intra-operative mechanical ventilation.

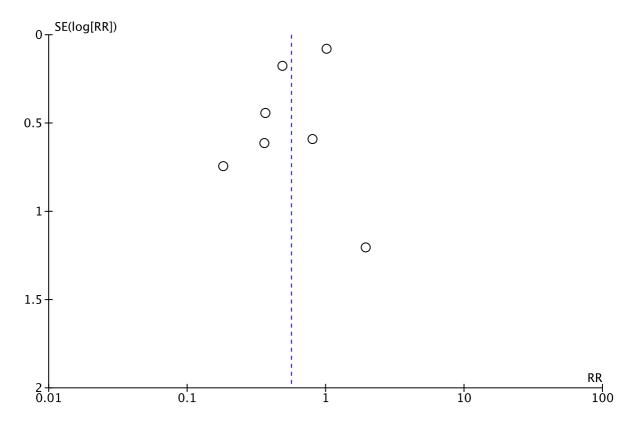


Figure 5.5 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of lung protective ventilation.

6. Prophylactic non-invasive ventilation

Study Author and	Study Sample and		Timing of		
Year	Country	Intervention description	Intervention F	Pulmonary Outcomes	Risk of bias

Delivery

	1	1	ı	Т	
		2 cycles of helmet CPAP for 120 min,			
		alternating with air-entrainment mask			
		oxygen therapy (at FiO2 0.4) every 4			
	n=50, Italy, single	hours; post operatively for the first day		Composite PPC, respiratory	
Barbagallo 2012	centre	only	Post-operative	infection	Poor
		Nasal CPAP with mask pressure of 10			
		cm H2O. Initial FiO2 of 0.4			
		thereafter adjusted according to the			
	n=204, Germany,	arterial blood gas analyses to achieve		Respiratory infection,	
Böhner 2002	single centre	oxygen saturation >95%.	Post-operative	respiratory failure	Poor
		5 to 15 cmH20 CPAP given			
	n=51, Denmark,	preoperatively and continued during	Pre-operative and		
Christensen 1991	single centre	postoperative period for 3 days.	post-operative	Composite PPC	Poor
Christensen 1991	single centre	Two groups received CPAP for either 15	post operative	Composite 11 C	1 001
		min or 30 min 4 times a day. 10 cm H2O			
	n=50, Australia,	on 30% oxygen at a total flow rate of 30			
Denehy 2001	single centre	l/min.	Post-operative	Composite PPC	Poor
Delicity 2001	single centre		rost-operative	Composite FFC	F 001
		High-flow nasal CPAP at 50–60 L/min.			
		In each group, oxygen flow was titrated			
		by the bedside nurse to maintain a			
		peripheral oxygen saturation of 95 % or			
		more. Allocated therapy was delivered		Composite PPC, respiratory	
	n=206, France,	continuously until 7.00-8.00 a.m. on		infection, respiratory	
Futier 2016	multi-centre	post-operative day 1	Post-operative	failure, atelectasis	Fair
		CPAP (8–12 cm H2O) for at least 8h on		Respiratory infection,	
	n=46, Egypt,	the first postoperative day; applied		respiratory failure,	
Hewidy 2016	single centre	immediately following extubation	Post-operative	atelectasis	Poor
Tie widy 2010	Single centre	Following extubation in the ICU,	1 ost operative	utoreetusis	1 001
		oxygen therapy was applied at ambient			
		pressure via a non-occlusive facemask			
		and intermittent mask CPAP therapy at a			
		pressure of 10 cm H2O every 4 h for 10			
Vindoon Millos	n=50, Germany,	min; duration of between 12 and 24 h		Composite PPC, respiratory	
Kindgen-Milles 2005	single centre	following extubation	Post-operative	infection, atelectasis	Poor
2003	single centre	Bilevel pressure support ventilation	rost-operative	infection, atelectasis	F 001
		provided for 1 h x6/d. Physicians were			
		responsible for prophylactic NIV			
		implementation, which included choice			
		and fitting of masks, adjustment of			
	260 F	ventilator settings, and initial patient		G : PPG :	
T + 2014	n=360, France,	adjustment. Maintained daily whilst an	D	Composite PPC, respiratory	D
Lorut 2014	multi-centre	inpatient.	Post-operative	infection, respiratory failure	Poor
		BiPAP for 7 days preoperatively - IPAP			
		was initially set at 8cmH2O and then			
		was increased until the maximal level			
		tolerated by the patient was reached.			
		EPAP was set at 2–4cmH2O.			
		Postoperatively, the same NIPSV			
		regimen was required with the exception			
		of the first 2 h following surgery during			
	n=32, France,	which the patients were not wearing	Pre-operative and		
Perrin 2007	single centre	NIPSV.	post-operative	Atelectasis	Fair
		High-flow nasal CPAP at 35 to 60 L/min			
		and FiO2 was titrated (from 45% to			
		100%) by the treating clinician to		Respiratory infection,	
	n=110, China,	maintain a peripheral SpO2 of 95% or		respiratory failure,	
Yu 2016	multi-centre	more.	Post-operative	atelectasis	Poor
	•			•	

	Experim	ental	Conti	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Christensen 1991	3	34	4	17	9.9%	0.38 [0.09, 1.49]	1991	
Denehy 2001	3	32	4	18	9.9%	0.42 [0.11, 1.68]	2001	
Böhner 2002	5	99	17	105	15.2%	0.31 [0.12, 0.81]	2002	
Kindgen-Milles 2005	7	25	24	25		Not estimable	2005	
Perrin 2007	2	14	7	18	9.6%	0.37 [0.09, 1.50]	2007	
Barbagallo 2012	10	25	8	25	18.9%	1.25 [0.59, 2.64]	2012	- •
Lorut 2014	57	181	55	179	27.5%	1.02 [0.75, 1.39]	2014	+
Hewidy 2016	2	24	7	22	9.1%	0.26 [0.06, 1.13]	2016	
Total (95% CI)		409		384	100.0%	0.59 [0.35, 1.00]		•
Total events	82		102					
Heterogeneity: Tau ² =	0.24; Chi ²	= 13.2	4, df = 6	(P = 0)	$.04$); $I^2 =$	55%		0.01 0.1 1 10 100
Test for overall effect:	Z = 1.96 (P = 0.0	5)					Favours [experimental] Favours [control]

Figure 6.1. Forest plot comparing proportions of patients developing PPCs in RCTs of prophylactic non-invasive ventilation (bilevel and CPAP) with oxygen administered at ambient pressure.

	Experim	ental	Conti	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Christensen 1991	3	34	4	17	16.1%	0.38 [0.09, 1.49]	1991	
Denehy 2001	3	32	4	18	16.1%	0.42 [0.11, 1.68]	2001	
Böhner 2002	5	99	17	105	23.8%	0.31 [0.12, 0.81]	2002	
Kindgen-Milles 2005	7	25	24	25	0.0%	0.29 [0.15, 0.55]	2005	
Barbagallo 2012	10	25	8	25	28.9%	1.25 [0.59, 2.64]	2012	-
Hewidy 2016	2	24	7	22	15.0%	0.26 [0.06, 1.13]	2016	
Total (95% CI)		214		187	100.0%	0.49 [0.24, 0.99]		•
Total events	23		40					
Heterogeneity: Tau ² =	0.30; Chi ²	= 7.68	, df = 4	(P = 0.1)	$(10); I^2 = 4$	8%		0.01 0.1 1 10 100
Test for overall effect:	Z = 1.99 (P = 0.0	5)					Favours [experimental] Favours [control]

Figure 6.2. Forest plot comparing proportions of patients developing PPCs in RCTs of prophylactic CPAP with oxygen administered at ambient pressure.

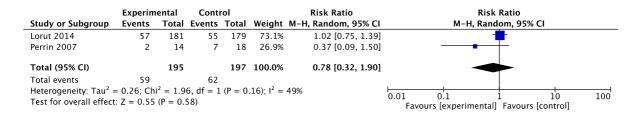


Figure 6.3. Forest plot comparing proportions of patients developing PPCs in RCTs of bilevel non-invasive ventilation with oxygen administered at ambient pressure.

	•		cperimental Control			Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% CI	
Futier 2016	19	108	21	112	86.5%	0.94 [0.54, 1.65]	-	
Yu 2016	2	56	5	54	13.5%	0.39 [0.08, 1.90]		
Total (95% CI)		164		166	100.0%	0.83 [0.46, 1.51]	•	
Total events	21		26					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 1.07$, $df = 1$ (P = 0.30); $I^2 = 6\%$						6%	0.01 0.1 1 10	100
Test for overall effect	z = 0.60	(P = 0.	55)				Favours [experimental] Favours [control]	100

Figure 6.4. Forest plot comparing proportions of patients developing PPCs in RCTs of prophylactic high flow nasal cannula oxygen with oxygen administered by air entrainment devices (nasal prongs or facemask).

	Experim	ental	Conti	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Böhner 2002	2	99	5	105	14.5%	0.42 [0.08, 2.14]	2002	
Kindgen-Milles 2005	0	25	3	25	5.0%	0.14 [0.01, 2.63]	2005	
Barbagallo 2012	0	25	3	25	5.0%	0.14 [0.01, 2.63]	2012	
Lorut 2014	29	181	28	179	68.0%	1.02 [0.64, 1.65]	2014	-
Hewidy 2016	1	24	2	22	7.5%	0.46 [0.04, 4.71]	2016	•
Total (95% CI)		354		356	100.0%	0.70 [0.36, 1.36]		•
Total events	32		41					
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 4.61$, $df = 4$ ($P = 0.33$); $I^2 = 13\%$						3%		0.01 0.1 1 10 100
Test for overall effect:	P = 0.2	9)					Favours [experimental] Favours [control]	

Figure 6.5. Forest plot comparing proportions of patients developing respiratory infection in RCTs of prophylactic non-invasive ventilation (bilevel and CPAP) with oxygen administered at ambient pressure.

	Experimental		Conti	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Futier 2016	19	108	21	112	86.5%	0.94 [0.54, 1.65]	-
Yu 2016	2	56	5	54	13.5%	0.39 [0.08, 1.90]	-
Total (95% CI)		164		166	100.0%	0.83 [0.46, 1.51]	•
Total events	21		26				
Heterogeneity: Tau2 =	= 0.03; Ch	$i^2 = 1.0$	7, df = 1	(P = 0)	$.30$); $I^2 =$	6%	0.01 0.1 1 10 100
Test for overall effect	Z = 0.60	(P = 0.	55)				Favours [experimental] Favours [control]

Figure 6.6. Forest plot comparing proportions of patients developing respiratory infection in RCTs of prophylactic high flow nasal cannula oxygen with oxygen administered by air entrainment devices (nasal prongs or facemask).

	Expe	erimer	ıtal	c	ontrol			Mean Difference			Mean Differe	nce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year		IV, Random, 95	5% CI	
Denehy 2001	12.5	4.8	32	12.3	4.8	18	21.2%	0.20 [-2.57, 2.97]	2001		+		
Böhner 2002	9.45	6.79	99	11.81	18.61	105	19.9%	-2.36 [-6.16, 1.44]	2002		-		
Kindgen-Milles 2005	22	2	25	34	5	25	21.9%	-12.00 [-14.11, -9.89]	2005		•		
Perrin 2007	12	1	14	19	3	18	22.4%	-7.00 [-8.48, -5.52]	2007		•		
Lorut 2014	18.6	40.7	181	16	30.3	179	14.5%	2.60 [-4.81, 10.01]	2014		+		
Total (95% CI)			351			345	100.0%	-4.25 [-8.90, 0.40]			•		
Heterogeneity: $Tau^2 = 24.55$; $Chi^2 = 59.23$, $df = 4$ (P < 0.00001); $I^2 = 93\%$										-100 -50	<u> </u>	50	100
Test for overall effect:	9 (P =	0.07)							nerimentall Favo		100		

Figure 6.7. Forest plot comparing hospital length of stay in RCTs of prophylactic non-invasive ventilation with oxygen administered at ambient pressure.

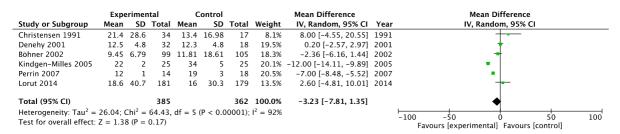


Figure 6.8. Forest plot comparing mortality in RCTs of prophylactic non-invasive ventilation with oxygen administered at ambient pressure.

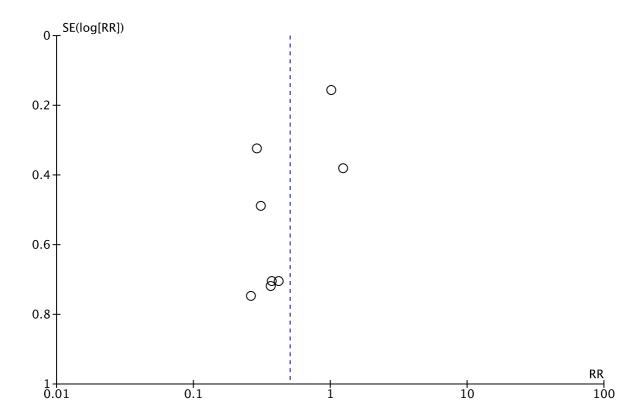


Figure 4.3 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of prophylactic non-invasive ventilation.

7. Analgesia

Study Author and Year	Study Sample and	Intervention description	Timing of Intervention	Pulmonary Outcomes	Risk of bias
Boisseau 2001	n=50, France, single centre	Intervention description T4/5 Thoracic epidural, continuous infusion of ropivicaine 0.2% with sufentanil 1 or 0.5 micrograms per ml started 1 hour befor the end of surgery	Intra-operative and post-operative	Composite PPC, respiratory infection and atelectasis	High risk
Esmea 2012	n=45, Turkey, single centre	At the end of the operation and every 4 h thereafter, the patients received 1.5 mg kg-1 bupivacaine epidural boluses	Intra-operative and post-operative	Composite PPC, atelectasis and pulmonary infection	High risk
Fleron 2003	n=217, France, single	1 microgram/kg sufentanil with 8 micrograms/kg preservative-free morphine injected at the L4/5 interspace	Pre-operative	Respiratory infection, atelectasis and respiratory failure	High risk
Lee 2016	n=100, South Korea, single centre	Dexmedetomidine loading dose 1mcg/kg IV for 20 mins prior to end of surgery	Intra-operative	Pulmonary function	High risk
Mann 2000	n=70, France, single centre	Continuous intraoperative epidural infusion of a 0.25% bupivacaine and 1-mcg/ml sufentanil mixture, followed by postoperative administration of a 0.125% bupivacaine and 0.5mcgg/ml sufentanil mixture provided with a PCEA pump programmed to deliver a 2- or 3-ml bolus with a lockout interval of 12 min and a background infusion of 3-5 ml/h.	Intra-operative and post-operative	Composite PPC and atelectasis	High risk

Norris 2001 n=79, USA, single centre Compositive patient controlled intravenous centre Compositive patient controlled intravenous post-operative and post-ope			Epidural (preoperative bolus and			
n=79, USA, single n=1021, USA, non-third non-t					Respiratory	
Norris 2001 Norris 2001 Centre Continuous lumbar or thoracic epidural anesthesia using 0.5% buptivaciane with epinephrine. Epidural morphine (0.5 mg/ml., 3-6 mg) immediately before or after surgery. Additional epidural morphine (0.5 mg/ml., 3-6 mg) immediately before or after surgery. Additional epidural morphine (0.5 mg/ml., 3-6 mg) immediately before or after surgery. Additional epidural morphine (0.5 mg/ml., 3-6 mg) immediately before or after surgery. Additional epidural morphine of 0.1-0.15 m.l.g.s. Neural blockade was ministanted during surgery with additional 5 ml. of levoluptivacaine 0.5% to a maximum of 0.1-0.15 m.l.g.s. Neural blockade was ministanted during surgery with additional 5 ml. of levoluptivacaine 0.5% to a maximum of 0.1-0.15 m.l.g.s. Neural blockade was ministanted during surgery with additional 5 ml. of levoluptivacaine 0.5% duministered lumbury. In the continuous interest of the morphine of the continuous interest of the continuous interest of the morphine of the continuous interest of the continuous						
Nomis 2001 Centre Or epidural analgesia Continuous imbar or thoracic epidural anesthesia using 0.5% bupivacaine with epinephrine. Fighdural morphise (3-6 mg) immediately before or after surgery. Additional epidural morphine (3-6 mg) was given every 12 to 24 hours, or mg) interestional objects of an amaintment of the surgery. Additional epidural morphine (3-6 mg) was given every 12 to 24 hours, or mg) interestional objects of an amaintment of unit levolupivacaine 0.5% to a maximum of 0.1-0.15 m/kg. Neural blockade was maintained during surgery with additional 5 ml. of levolupivacaine 0.25% administered hourly. Epidural infusion of levolupivacaine 0.25% administered hourly. Lipidural furings or increvency and lot ml./ started at the end of surgery and lot ml./ started at the end of surgery and lot ml./ started at the end of surgery and lot ml./ started at the end of surgery and ministered hourly administered hourly administered hourly postoperative period of 30 min in the 24 hours postoperative propostoperative period of 30 min in the 24 hours postoperative propostoperative period of 30 min in the 24 hours postoperative propostoperative period of 30 min in the 24 hours postoperative and post-operative propostoperative period of 30 min in the 24 hours postoperative propostoperative period of 30 min in the 24 hours postoperative propostoperative period of 30 min in the 24 hours postoperative propostoperative period of 30 min in the 24 hours postoperative propostoperative period of 30 min in the 24 hours postoperative and post-operative and p		n=79, USA, single		Intra-operative and		
anesthesia using 0.5% bupivacaine with epinephrine. Figural morphine (3-6 mg) immediately before or after surgery. Additional epidural morphine (3-6 mg) was given every 12 to 24 hours, or multi-centre Radovanovic n=60. Serbia. Radovanovic n=60. Serbia. 2017 single centre n=10. Turkey. Sen 2009 n=10. Turkey. Sen 2009 n=10. Turkey. Sen 2009 n=10. Turkey. Sen 2009 n=60. Turkey. Sen 2007 n=60. Turkey. Sen 2008 n=	Norris 2001			*	failure	Low risk
epinephrine. Epidural morphine (0.5 mg/ml, 3-6 mg) immediately before or after surgery. Additional epidural morphine (0.5 mg) was given every 12 to 24 hours, or continuously, for as long as it was needed. T8-T12 epidural catheter with Levobupitvacaine 0.5% to a maximum of 0.1- 0.15 mL/kg. Neural blockade was maintained during surgery with additional 5 ml. of levobupivacaine 0.2% administered hourly. Epidural infusion of bevobupivacaine 217 mse82, Australia, East-Asia and Middle East, multicentre Raging 2002 m=10, Turkey, 2014 T1-6, Turkey, 2014 T1-6, Turkey, 2014 T1-6, Turkey, 2015 I1-70, Turkey, 2016 I1-70, Turkey, 2017 Sen 2009 m=10, Turkey, 2017 T1-6, Turkey, 2017 T1-70, Turkey, 2017 T1-70, Turkey, 2017 I1-70, Turkey, 2018 m=60, China, aingle centre T1-70, Turkey, 2017 I1-70, Turkey, 2017 I1-70, Turkey, 2017 I1-70, Turkey, 2018 m=10, Turkey, 2019 I1-70, T				•		
Park 2001 Indicenter Indi						
surgery. Additional epidural morphine (3-6 mg) was give nevery 12 to 24 hours, or continuously, for as long as it was needed. T8-T12 epidural catheter with Levobuptivacaine 0.5% to a maximum of 0.1 to 1.5 mL/sg. Reural blockade was maintained during surgery with additional 5 mL of levobuptivacaine 0.2% administered hourly. Epidural infinitional 5 mL of levobuptivacaine 0.2% administered and adrealine 2 µg/mL at a rate between 5 and 10 mL/s hastned at the end of surgery and continued up to postoperative day 3. Radovanovic and 10 mL/s hastned at the end of surgery and continued up to postoperative day 3. Rigg 2002 m10. Trivey. Sagrioglu n=110. Turkey, single centre						
Park 2001 multi-centre					Respiratory	
Park 2001 multi-centre Continuously, for as long as it was needed. T8-T12 epidural enthere with Levobuplyvacaine 0.5% to a maximum of 0.1					infection and	
TS-T12 epidural catheter with Levobupivacaine 0.5 % to a maximum of 0.1- 0.15 mL/kg. Neural blockade was maintained during surgery with additional 5 mL of levobupivacaine 0.25% administered hourly. Epidural infusion of levobupivacaine 1 mg/mL with frentanyl 3 µg/mL and adrenaline 2 µg/mL at a rate between 5 and 1 on L/h started at the end of surgery and continued up to postoperative day 3. Pre-operative, intra-operative and post operative and post operative epidural analgesia for 72 hours with didle East, single centre T4-6, Patein Controlled epidural analgesia for 72 hours with a feat to end of surgery and continued up to postoperative day 3. Rigg 2002						
Levobupivacaine 0.5% to a maximum of 0.1- 0.15 mL/g. Neural blockade was maintained during surgery with additional 5 mL of levobupivacaine 0.25% administered hourly. Epidural infusion of levobupivacaine 0.25% administered hourly. Epidural infusion of levobupivacaine 1 mg/ml. with fentanyl 3 µg/ml. and adrenaline 2 µg/ml. at a rate between 5 and 10 mL/s stared at the end of surgery and continued up to postoperative day 3. 10 mL/s stared at the end of surgery and continued up to postoperative day 3. 10 mL/s stared at the end of surgery and continued up to postoperative day 3. 10 mL/s stared at the end of surgery and continued up to postoperative day 3. 10 mL/s, and a decension of the continued up to postoperative and post-operative an	Park 2001	multi-centre		operative	failure	High risk
Radovanovic n=60, Serbia, single centre						
maintained during surgery with additional 5 mL of tevobupivacaine 0.25% administered hourly. Epidural infusion of fevobupivacaine 1 mg/mL with fentanyl 3 µg/mL and adrenaline 2 µg/mL at a rate between 5 and 10 mL/m starred at the end of surgery and continuous up to postoperative day 5. Radovanovic and maintained 2 µg/mL at a rate between 5 and 10 mL/m starred at the end of surgery and continuous up to postoperative day 5. Rigg 2002 maintained East, multicentre maintained East, and Middle East, multicentre mount operative and post-operative epidural analgesia for 72 hours mount operative and post-operative and post-operative protocol of the post-operative mintra-operative and post-operative mintra-operative min						
M. of tevobupivacaine 0.25% administered hourly. Epidural infixion of fevobupivacaine 1 mg/mL with fentanyl 3 µg/mL and adrenaline 2 µg/mL at a rate between 5 and 10 mL/h started at the end of surgery and continued up to postoperative day 3. Rigg 2002			e e e e e e e e e e e e e e e e e e e			
Radovanovic n=60, Serbia, single centre						
Radovanovic n=60, Serbia, single centre n=82, Australia, East-Asia and Middle East, multicentre postoperative day 3. Rigg 2002 militentre postoperative day 3. Rigg 2002 moliticentre postoperative day 3. Rigg 2002 moliticentre postoperative day 3. Sagrioglu n=110, Turkey, single centre postoperative period nin the 24 hours post-operative militarion nin the 24 hours post-operative period nin the 24 hours post-operative ninteral of 30 min in the 24 hours post-operative ninteralors nin the 24 hours post-operative period nin the 24 hours post-operative period nin the 24 hours post-operative ninteralors ninteral of 30 min in the 24 hours post-operative period ninteral of 30 min in the 24 hours post-operative prost-operative period ninteral of 30 min in the 24 hours post-operative ninteralors ninteral of 30 min in the 24 hours post-operative ninteralors ninteral of 30 min in the 24 hours post-operative ninteralors nintera						
Radovanovic 2017 adrenatine 2 µg/mL. at a rate between 5 and 10 m.H. starded at the end of surgery and continued up to postoperative day 3. Rigg 2002 Middle East, Missing and Missing and Middle East, Missing and Missing and Missing and Missing a						
Radovanovic n=60, Serbia, a n=70, Turkey, single centre n=70, Turkey, single centre n=60, China, singl				Dra aparativa intra		
Sagrioglu Description De	Radovanovic	n=60 Serbia				
Rigg 2002 Rigg				• •	Composite PPC	High risk
Rigg 2002 East-Asia and Middle East, mullicentre General anaesthesia with intraoperative and postoperative epidural analgesia for 72 hours T4-6, Patient Controlled epidural analgesia 0.1 mL/kg/h, with 2 mL on demand, and a lock-out interval of 30 min in the 24 hours 2014 single centre postoperative period 1 g (2 ml) etofenamate intramuscularly, and including the postoperative Post-operative Post-operative Respiratory infection, and atelectasis High risk T4-6, Patient Controlled epidural analgesia Post-operative Post-operative Pre-operative Respiratory infection, and atelectasis High risk T4-6, Patient Controlled epidural analgesia Post-operative Pre-operative Pre-o	2017		continued up to postoperative day 3.	орегинче	Composite 11 C	THE THE
Middle East, multicentre General anaesthesia with intraoperative and postoperative epidural analgesia for 72 hours		· ·				
Rigg 2002 mulitcentre postoperative epidural analgesia for 72 hours T4-6, Patient Controlled epidural analgesia O.1 mL/kg/h, with 2 mL on demand, and a lock-out interval of 30 min in the 24 hours single centre postoperative period Post-operative Post-operative Respiratory infection, atelectasis, reintubation High risk			General anaesthesia with intraoperative and	intra-operative and	Respiratory	
Sagrioglu 2014	Rigg 2002	mulitcentre		<u> </u>		High risk
Sagrioglu 2014				•		Ü
2014 single centre postoperative period Post-operative reintubation High risk						
Sen 2009 n=70, Turkey, single centre		n=110, Turkey,				
Sen 2009 single centre 1 g (2 ml) etofenamate intramuscularly, administered 1 hour before surgery Pre-operative Pre-operative Pre-operative High risk	2014	single centre	postoperative period	Post-operative	reintubation	High risk
Sen 2009 single centre 1 g (2 ml) etofenamate intramuscularly, administered 1 hour before surgery Pre-operative Pre-operative Pre-operative Pre-operative High risk					Respiratory	
Sen 2009 single centre administered 1 hour before surgery Pre-operative atelectasis High risk		n=70. Turkey.	1 g (2 ml) etofenamate intramuscularly.			
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Yildrim 2007			mL ropivacaine 0.2% during a 30-min			
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2007 single centre minimum of 3 days. T8-9 epidural. Iinfusion of 0.05 % bupivacaine and 100 Ig/mL morphine at 4 mL/h for 48 h, supplemented by rescue boluses of 4 mL, with a 30-min lock-out period, using an electronic patient-controlled analgesia (PCA) pump. Garnett n=99, Canada, single epidural (BA + Lumbar epidural (bupivacaine 0.1% + meperidine 2 mg/ml) at 5-15 ml/h. Davies Australia, bolus each hour. Infusion rate not single specified. Kilbride n=43, USA, single Lumbar epidural Equivacaine 0.1% + fentanyl 0.001% at 5-8 ml/h initiated at least 30 min before anticipated Migh risk High risk at least 4 mL/h for 48 h, supplemented by rescue boluses at 4 mL/h for 48 h, supplemented by rescue boluses at 4 mL/h for 48 h, supplemented by rescue boluses of 4 mL, with a 30-min lock-out period, using and 100 Ig/mL morphine at 4 mL/h for 48 h, supplemented by rescue boluses of 4 mL, with a 30-min lock-out period, using and 100 Ig/mL morphine at 4 mL/h for 48 h, supplemented by rescue boluses of 4 mL, with a 30-min lock-out period, using and 100 Ig/mL morphine at 4 mL/h for 48 h, supplemented by rescue boluses of 4 mL, with a 30-min lock-out period, using and electronic patient-controlled analgesia (PCA) pump. Post-operative Pulmonary infection High risk Intra-op, post- operative probable post-operative probable post-operative probable post-operative infection operative probable prob						
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mL/h for 48 h, supplemented by rescue boluses of 4 mL, with a 30-min lock-out period, using an electronic patient-controlled analgesia (PCA) pump. Garnett n=99, Canada, single epidural (BA + Lumbar epidural (Baptical (Baptica						
Davies Davies Davies Single Single Davies Single Single Davies Single Single Single Davies Single S						
n=60, China, single centre period, using an electronic patient-controlled analgesia (PCA) pump. Post-operative Pulmonary infection High risk						
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Garnett n=99, Canada, single epidural (bupivacaine 0.1% + Intra-op, post-op infection High ri n=50,	7hu 2012			Post operative	•	Uigh riek
Garnett n=99, Canada, single epidural (bupivacaine 0.1% + meperidine 2 mg/ml) at 5-15 ml/h. Thoracic epidural (T9-10) with n=50,	Ziiu 2013	single centre		1 ost-operative	infection	High lisk
1996 single meperidine 2 mg/ml) at 5-15 ml/h. op infection High ri Thoracic epidural (T9-10) with 0.5% bupivacaine at a rate of 5ml bolus each hour. Infusion rate not specified. Kilbride n=43, USA, single Lumbar epidural Lumbar and thoracic epidural. Bupivacaine 0.1% + fentanyl 0.001% at 5-8 ml/h initiated at least 30 min before anticipated Bupivacaine 0.1% + fentanyl 0.001% at 5-8 ml/h initiated at least 30 min before anticipated	~	00 0 1		.		
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n=50, Australia, single n=43, USA, single n=43, USA, single Lumbar epidural Lumbar and thoracic epidural. Bupivacaine 0.1% + fentanyl 0.001% at 5-8 ml/h initiated at least 30 min before anticipated n=50, Australia, bolus each hour. Infusion rate not specified. Intra-op, post- op infection, prolonged ventilation concern Intra-op, post- op infection, prolonged ventilation concern	1996	single	meperidine 2 mg/ml) at 5-15 ml/h.	op	infection	High risk
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Lumbar and thoracic epidural. Bupivacaine 0.1% + fentanyl 0.001% at 5-8 ml/h initiated at least 30 min before anticipated			l			
Bupivacaine 0.1% + fentanyl 0.001% at 5-8 ml/h initiated at least 30 min before anticipated	1992	single		op	infection	concerns
Bupivacaine 0.1% + fentanyl 0.001% at 5-8 ml/h initiated at least 30 min before anticipated			Lumbar and thoracic epidural.			
0.001% at 5-8 ml/h initiated at least 30 min before anticipated						
30 min before anticipated						
m 00 TYG4 1 1 C1 1 1		00 ***				
Tuman n=80, USA, completion of the surgical Intra-op, post-				Intra-op, post-		
1991 single procedure op PPC High ri	1991	single	procedure	op	PPC	High risk

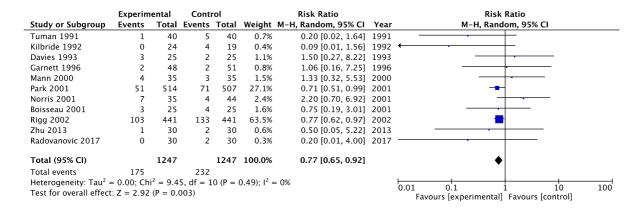


Figure 7.1. Forest plot comparing proportions of patients developing PPCs in RCTs of epidural analysesia therapies against morphine patient controlled analysesia.

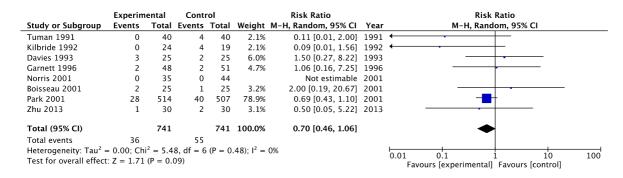


Figure 7.2. Forest plot comparing proportions of patients developing respiratory infections in RCTs of epidural analgesia therapies against morphine patient controlled analgesia.

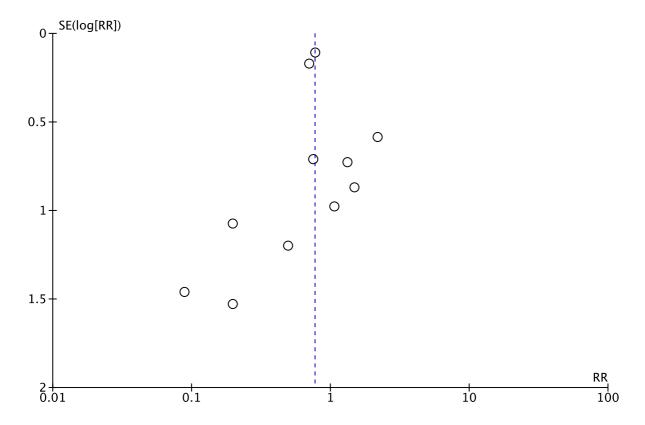


Figure 7.3 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of epidural analgesia.

8. Lifestyle modifications

Study Author	Study Sample and		Timing of Intervention	Pulmonary	D. 1 . 61.
and Year	Country	Intervention description	Delivery	Outcomes	Risk of bias
Lindström 2008	n=102, Sweden, single centre	Weekly sessions, face-to-face or by telephone, with a trained smoking cessation counsellor and nicotine replacement therapy 4 weeks preand 4 weeks postoperatively.	Pre-operative and post-operative (smoking cessation)	Composite PPC	High risk
Møller 2002	n=102, Denmark, multi-centre	Pre-operative smoking intervention was weekly nurse-led counselling and nicotine replacement therapy	Pre-operative (smoking cessation)	Respiratory failure	High risk
Sorensen 2003	n=57, Denmark, single-centre	2-3 weeks before surgery, patients were given smoking cessation advice, nurse-led counselling and nicotine replacement	Pre-operative (smoking cessation)	Respiratory infection, respiratory failure	Some concerns
Wong 2012	n=304, Canada, single centre	Varenicline initiated 1 week before the target quit date (24 hours before surgery) and continued for a total of 12 weeks	Pre-operative and post-operative (smoking cessation)	Composite PPC	Some concerns

	Experim	Experimental Control				Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Møller 2002	1	56	1	52	15.8%	0.93 [0.06, 14.47]	2002	
Sorensen 2003	3	27	4	30	60.6%	0.83 [0.20, 3.39]	2003	
Lindström 2008	0	48	1	54	11.8%	0.37 [0.02, 8.97]	2008	
Wong 2012	1	151	0	153	11.7%	3.04 [0.12, 74.03]	2012	•
Total (95% CI)		282		289	100.0%	0.90 [0.30, 2.68]		
Total events	5		6					
Heterogeneity: Tau2 =	= 0.00; Ch	$i^2 = 0.8$	6, df = 3	(P = 0)	$.83$); $I^2 = 0$	0%		0.01 0.1 1 10 100
Test for overall effect	(P = 0.3)	85)					Favours [experimental] Favours [control]	

Figure 8.1 Forest plot comparing proportions of patients developing PPCs in RCTs of smoking cessation therapies against standard medical care.

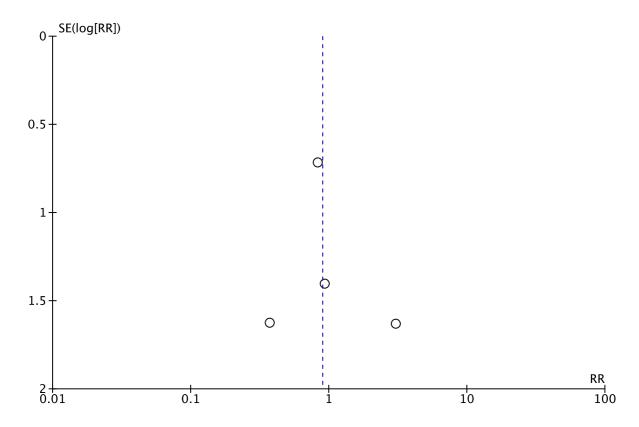


Figure 8.2 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of smoking cessation therapies.

9. Enhanced post-operative recovery pathways

Study			Timing of		
Author and	Study Sample and		Intervention	Pulmonary	
Year	Country	Intervention description	Delivery	Outcomes	Risk of bias
		Modified fast-track protocol consisting of:			
		Pre-op: Intake of 1000 mL 14% carbohydrate			
		drink 12 h before and 350 mL 14%			
		carbohydrate drink 3 h before surgery. Intra-			
		op: tracheal intubation and general anesthesia,			
		thermal insulation of the body and extremities,			
		body temperature was maintained at 36 °C;			
		standard laparotomy approach; no routine use			
		of abdominal drainage tube; infiltration of			
		surgical wounds with ropivacaine at the end of			
		surgery and 24 h after surgery. Post-op: Oral			
		intake of 200 mg celecoxib twice daily,			
		encourage patients to mobilize out of bed, oral			
		intake of 500-1000 mL glucose saline on the			
		day of surgery, intake of 2000-3000 mL liquid			
		food containing 1000 kcal to 1200 kcal per			
		day from the 1st day after surgery, infusion of			
		parenteral nutrition (25 kcal/kg of body			
		weight) iv before oral intake. Appropriate			
		level of iv fluid intake based on the volume of			
		liquid intake and output and physiological			
		need. Infusion of parenteral nutrition iv if oral	Pre-operative, intra-		
	n=119, China,	intake is not adequate. Appropriate level of iv	operative and post-	Respiratory	
Feng 2013	single centre	fluid intake based on the volume of liquid	operative	infection	High risk

		1	ı	1	
		intake and output, and physiological need;			
		removal of nasogastric tube within 24 h after			
		surgery; removal of urine catheter within 24 h			
		after surgery; standard use of antibiotics			
		before and once after surgery			
		Protocolised evidence based pre-, intra- and			
		post-op care pathway consistent with ERAS			
		guidelines. Pre-op: Information and			
		counselling, optimisation of organ function,			
		smoking and alcohol abstinence, no bowel			
		preparation, carbohydrate loading			
		Intraoperative: Fluid optimisation,			
		maintenance of normothermial, regional			
		anesthesia where possible, short-acting			
		opioids, minimally invasive surgery, oxygen			
		therapy, antibiotic prophylaxis,			
		thromboprophylaxis			
		Postoperative: Multimodal and opioid-			
		sparing analgesia, prevention of nausea and			
		vomiting, prevention of ileus, early enteral	Pre-operative, intra-	Composite PPC,	
Gonenc	n=47, Turkey,	nutrition, early mobilization, early removal of	operative and post-	pleural effusion,	
2014	single centre	catheters, drains, and tubes, discharge criteria	operative	atelectasis	High risk
HIP		Accelerated surgical procedure and			
ATTACK	n=60, multi-	accelerated medical clearance of fitness for			
investigators	national, multi-	surgery, with a goal of surgery within 6 h of		Respiratory	
2014	centre	diagnosis	Pre-operative	infection	High risk
		Pre-op: bowel preparation with oral purgatives	•		Ü
		instead of amechanical enema. Intra-op:			
		thoracic epidural anesthesia and postoperative			
		analgesic maintenance via the epidural			
		catheter (ropivacaine, 2 mg/ml maintained for			
		48 h, controlled to 6–10 ml (12–20 mg) per			
		hour and opium-derived agents were			
		excluded, no nasogastric tube insertion, no			
		drainage tube placement with the exception of			
		low rectal anastomosis; Post-op: water was			
		allowed from 6 h post operation, liquid diet in			
		the morning and semi-liquid diet at noon and			
		evening of the first and second postoperative			
	100 011	days (POD) with regular diet on POD 3, early	Pre-operative, intra-		
	n=133, China,	urine catheter withdrawal (at POD1–2), early	operative and post-	Respiratory	
Jia 2014	single centre	out-of-bed mobilization (i.e., walking).	operative	infection	High risk
		Preoperatively inserted epidural catheter			
	1	which was placed in intervertebral spaces T5-			
	1	T6. At the end of surgery, 0.25% epidural			
	1	marcaine and 2µg/ml			
	1	fentanyl were infused. Marcaine (2-2.5			
	1	μg/hour) was transfused at the rate of			
	1	5ml/hour postoperatively via patient			
		controlled epidural analgesia (PCEA) in the			
		ICU. Diclofenac suppository (100 mg) was			
	1	also			
	1	administered when needed. Feeding and			
	1	ambulation			
		started the night after and one day after	Pre-operative, intra-	Composite PPC,	
Sokouti	n=60, Iran single	surgery,	operative and post-	pleural effusion,	
2011	centre	respectively.	operative and post-	atelectasis	High risk
2011	Centre	respectively.	орегануе	atelectasis	riigii IISK

	Experim	Experimental Control				Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI			
Sokouti 2011	5	30	17	30	35.2%	0.29 [0.12, 0.69]	2011				
Feng 2013	5	59	10	60	25.4%	0.51 [0.18, 1.40]	2013				
Jia 2014	6	117	19	116	33.5%	0.31 [0.13, 0.76]	2014				
Gonenc 2014	1	21	4	26	5.8%	0.31 [0.04, 2.56]	2014	· ·			
Total (95% CI)		227		232	100.0%	0.35 [0.21, 0.58]		•			
Total events	17		50								
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.75$, $df = 3$ (P = 0.86); $I^2 = 0$ %						0%					
Test for overall effect	(P < 0.	0001)					0.01 0.1 1 10 100 Favours [experimental] Favours [control]				

Figure 9.1. Forest plot comparing proportions of patients developing PPCs in RCTs of ERAS against standard post-operative care.

	Expe				ontro			Mean Difference		Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year		IV, Rando	m, 95% CI		
Sokouti 2011	3.8	1.9	30	6.9	2.2	30	29.1%	-3.10 [-4.14, -2.06]	2011		•			
Feng 2013	9	1.75	59	13.2	1.32	60	31.1%	-4.20 [-4.76, -3.64]	2013					
Jia 2014	8.5	7	21	8.6	12	26	8.5%	-0.10 [-5.60, 5.40]	2014		-	+		
Gonenc 2014	5.68	1.22	117	7.1	2.13	116	31.4%	-1.42 [-1.87, -0.97]	2014					
Total (95% CI)			227					-2.66 [-4.53, -0.79]			•)		
Heterogeneity: $Tau^2 = 2.84$; $Chi^2 = 60.10$, $df = 3$ (P < 0.00001); $I^2 = 95\%$ Test for overall effect: Z = 2.79 (P = 0.005)											-50 [experimental]	0 Favours [co	50 ntrol]	100

Figure 9.2. Forest plot comparing hospital length of stay in RCTs of ERAS against standard post-operative care.

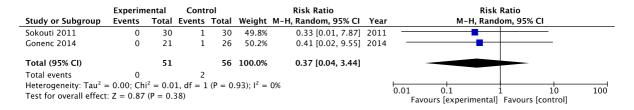


Figure 9.3. Forest plot comparing mortality in RCTs of ERAS against standard post-operative care.

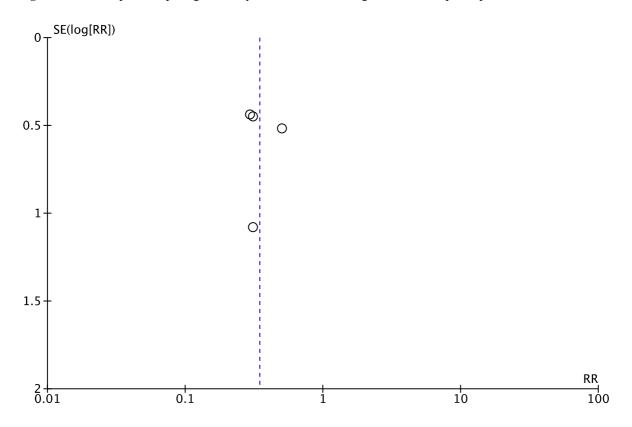


Figure 10.4 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of ERAS.

10. Perioperative fluid administration

Study			Timing of		
Author and	Study Sample and		Intervention		
Year	Country	Intervention description	Delivery	Pulmonary Outcomes	Risk of bias
		Restrictive = $<$ or = 2 L water and 77			
		mmol sodium per day. Liberal = > or =			
		3 L water and 154 mmol sodium per			Some
Lobo 2002	n=20, UK, single	day	Post-op	Respiratory infection	concerns
		Restrictive = Volume to volume			
		replacement with HES 6%. Liberal =			
		Pre-operative 0.9% NaCl 500ml +			
		volume to volume replacement +			
	150 5	7ml/kg/h for 1st hour then 5ml/kg/h for		Respiratory infection,	~
Brandstrup	n=172, Denmark,	2nd-3rd hours then 3ml/kg/h therafter of		pulmonary oedema,	Some
2003	multi centre	0.9% NaCl	Pre-op, intra-op	pneumothorax	concerns
		Restrictive = 1 mL/kg/h, nothing by			
	150	mouth and an intraoperative substitution			
	n=156, Switzerland,	of 5 mL/kg/h. Liberal = 2 mL and 10 mL/kg/h for preoperative loading and			Some
Muller 2009	multicentre	intraoperative substitution, respectively.	Pre-op, intra-op	Respiratory infection	concerns
Wither 2009	municentie		Tre-op, mira-op	Respiratory infection	Concerns
.	150 7 1	Restrictive = Hartman's 4 ml/kg/h.			
Nisanevich	n=152, Israel,	Liberal = 10 ml/kg/h prior to incision,	.	.	Some
2005	single	then 12 ml/kg/h maintenance	Intra-op	Respiratory infection	concerns
		Restrictive = 7 ml/kg/h for 1st hr; 5		Respiratory infection,	
	n=32, Denmark,	ml/kg/h subsequently. Liberal = 18		respiratory failure,	
Holte 2007	single	ml/kg/h	Intra-op, post-op	pulmonary oedema	Low risk
		Restrictive = 10ml/kg/h intraop, 5ml/kg			
		in PACU then 1L oral intake with IV			
		fluids only with clinical evidence of fluid deficit. Liberal = 175ml 6h per-op,			
		30ml/kg/h intraop, 5ml/kg in PACU			
	n=48, Denmark,	then 1L oral intake with IV fluids only			
Holte 2007	Single	with clinical evidence of fluid deficit.	Intra-op, post-op	Respiratory infection	Low risk
110110 2007	Single	with chinear evidence of fluid deficit.	mtra-op, post-op	Respiratory infection	LOWIISK
McArdle		D 4 4 10 0			G
2009	n=22, UK, single	Restrictive = Hartman's 4 ml/kg/h. Liberal = Hartman's 12 ml/kg/h	Intra-op	Respiratory infection	Some concerns
2009	II–22, UK, Sliigie	Liberal – Hartillali s 12 lill/kg/li	шиа-ор	Respiratory infection,	Concerns
				respiratory failure,	
	n=70, France,	Restrictive = 6 ml/kg/h. Liberal = 12		pulmonary embolism,	Some
Futier 2010	single	ml/kg/h.	Intra-op	pneumothorax	concerns
1 41101 2010	Jingie	Restrictive = 2 ml/kg/h from start of	ши ор	phoumonorus	Concomis
		anaesthesia, then 1 ml/kg/h from early			
		after operation until morning after			
		surgery. Liberal = 500ml-1000ml pre-			
		op, then 1000 ml infused in early			
Abraham-		postoperative period + 7 ml/kg/h, then			
Nordling	n=161, Sweden,	then 1 ml/kg/h from early after	Pre-op, intra-op,		Some
2012	single	operation until morning after surgery.	post-op	Respiratory infection	concerns

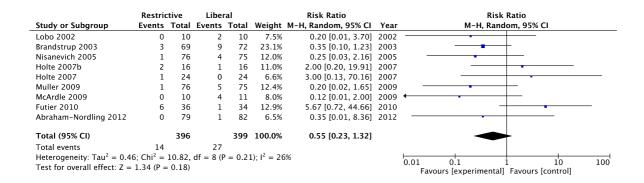


Figure 10.1. Forest plot comparing proportions of patients developing PPCs in RCTs of restrictive versus liberal fluid administration.

	Res	tricti	ve	Li	bera	I		Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Lobo 2002	6	0.5	10	9	1.6	10	17.0%	-3.00 [-4.04, -1.96]	2002	•
Nisanevich 2005	5	7	76	9	6	75	14.3%	-4.00 [-6.08, -1.92]	2005	•
Holte 2007b	3	8	16	4.7	5.7	16	7.4%	-1.70 [-6.51, 3.11]	2007	+
Holte 2007	4	3.8	24	4	0.5	24	15.8%	0.00 [-1.53, 1.53]	2007	<u> </u>
McArdle 2009	7.8	0.6	10	16	4.8	11	12.0%	-8.20 [-11.06, -5.34]	2009	+
Muller 2009	8	3.8	77	9	4.3	75	16.4%	-1.00 [-2.29, 0.29]	2009	•
Abraham-Nordling 2012	6	3	79	6	3	82	17.2%	0.00 [-0.93, 0.93]	2012	†
Total (95% CI)			292			293	100.0%	-2.35 [-4.05, -0.65]		♦
Heterogeneity: $Tau^2 = 4.1$	Heterogeneity: $Tau^2 = 4.13$; $Chi^2 = 48.94$, $df = 6$ (P < 0.00001); $I^2 = 88\%$									-100 -50 0 50 100
Test for overall effect: Z =	2.72 (P	= 0.0	007)							Favours [experimental] Favours [control]

Figure 10.2. Forest plot comparing hospital length of stay in RCTs of restrictive versus liberal fluid administration.

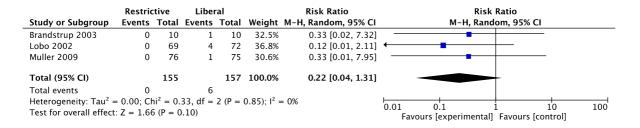


Figure 10.3. Forest plot comparing mortality in RCTs of restrictive versus liberal fluid administration.

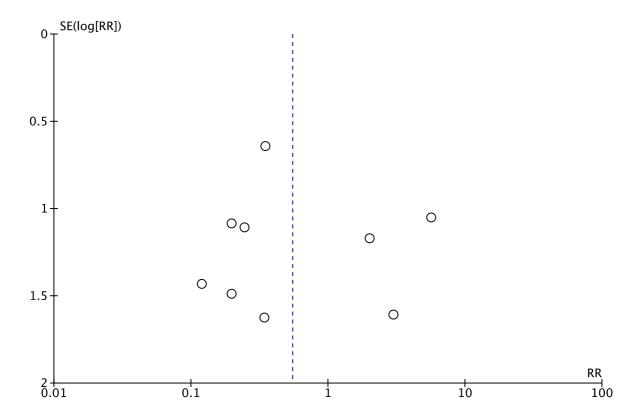


Figure 10.4 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of restrictive versus liberal fluid administration.

Carrier Arrahan	C41 C11		Timing of		
Study Author and Year	Study Sample and Country	Intervention description	Intervention Delivery	Pulmonary Outcomes	Risk of bias
				·	
Boyd 1993	n=107, single	Pulmonary artery catheter	Intra-op	Respiratory infection	High risk
		Pulmonary artery catheter. 1 litre of Hartmann's solution + Human			
		albumin solution 4.5% until a			
		pulmonary artery occlusion pressure of 12 mm Hg. 0.025 μg/kg/min for		Respiratory infection, ventilatory support for	
		adrenaline and 0.125 µg/kg/min for		>24h, pulmonary	
Wilson 1999	n=138, UK, single	dopexamine.	Intra-op, post-op	oedema	Low risk
		Pulmonary artery catheter. Fluid challenges for PAC patients with			
		PCWP less than 15 mm Hg consisted			
		of 9 ml/kg Ringer's lactate solution rapidly instilled through the central			
		venous pressure port. Additional fluid		Respiratory infection,	
** 1		boluses were given until the PCWP		ventilatory support for	G
Valentine 1998	n=120, single	was greater than 12 mm Hg or the subject received 3000 ml of fluid.	Intra-op, post-op	>24h, pulmonary oedema	Some concerns
	., g	Oesophageal Doppler. Fluid	FAR THE TE	Respiratory infection,	
C 2002	n=100, USA,	admistration guided by FTc and		ventilatory support for	Some
Gan 2002	single	stroke volume algorithm. Colloid fluid challenges guided by		>24h	concerns
		central venous pressure or			
Venn 2002	n=90, UK, single	oesophageal doppler (2 intervention groups)	Intra-op	Respiratory infection	Low risk
V CIIII 2002	n=90, CII, Single	Pulmonary artery catheter. Fluid	тиц ор	respiratory infection	Low Hak
		loading, inotropic therapy, vasodilator therapy, vasopressors for			
		hypotension, and blood transfusion			
		for a hematocrit of <27 %, in order to			
		achieve oxygen-delivery index of 550 to 600 ml per minute per square			
		meter of body-surface area, a cardiac			
		index of 3.5 to 4.5 liters per minute per square meter, a mean arterial			
		pressure of 70 mm Hg, a pulmonary-			
a "	1004 6	capillary wedge pressure of 18 mm			
Sandham 2003	n=1994, Canada, multi-centre	Hg, a heart rate of less than 120 beats per minute	Intra-op	Respiratory infection, pneumothorax	Some concerns
		250ml fluid bolus until sustained rise			
		in stroke volume of >10% achieved for 20 mins. Dopexamine up to a			
		maximum of 1µg/kg/min if oxygen		Respiratory infection,	
		delivery index (DO2I) did not reach 600 ml/min/m2 with intravenous		ARDS, pulmonary	
Pearse 2005	n=122, UK, single	fluid alone	Post-op	oedema, pulmonary embolism	Low risk
			-	PPC, Respiratory	
				infection, ventilatory support for >24h,	
		Change in pulse pressure variation.		Acute lung injury,	
Lopes 2007	n=33, Brazil, Single	HES fluid bolus to maintain $\Delta PP \le 10\%$	Intra-op	pulmonary embolism, pulmonary oedema	Some concerns
Eupes 2007	Single	Pulse contour analysis. Maintain the	шиа-ор	punnonary ocucina	CONCEINS
	n=120, Czech	stroke volume variation below 10%		Respiratory infection,	Some
Benes 2010	Republic, single	using colloid boluses of 3 ml/kg	Intra-op	ventilatory support PPC, Respiratory	concerns
		Pulse contour analysis (FloTrac).		infection, ventilatory	
May: 2010	n=60, Germany,	Fluid bolus to maintain cardiac index	Intro oc	support for >24h,	Some
Mayer 2010	single	≥ 2.5 Serum lactate level was monitored	Intra-op, post-op	pulmonary oedema	concerns
		closely inatra- and post-operatively to			
		maintain a normal pre-operative serum lactate level, with fluid		Respiratory infection, pneumothorax,	
	n=299, China,	adminstered to maintain serum lactate		pulmonary oedema,	Some
Wenkui 2010	single	<1.6 mmol/L Pulse contour analysis (FloTree) SV	Intra-op, post-op	pulmonary emboli	concerns
		Pulse contour analysis (FloTrac). SV was first maximised with fluid			
G :3011	n=40, UK, Italy,	challenges. Boluses of 250 mL of	T.	D	,
Cecconi 2011	single	HES were administered until the SV	Intra-op, post-op	Respiratory infection	Low risk

		failed to increase by a factor of 10%. If 25 mL/kg HES had been given before SV maximisation was achieved, fluid challenges were then performed with 250 mL boluses of Ringer's lactate solution. If at this stage the DO2I was not greater than 600 mL/m2, then dobutamine was started at a dose of 3 µg/kg/minute and increased by the same increment every 20 minutes to reach the described target. Pulse contour analysis (LiDCO			
		rapid). Intravenous colloid solution administered in 250mL boluses to achieve and maintain a maximal value of stroke volume; no attempt			
Pearse 2014	n=734, UK, multicentre	was made to standardize choice of colloid. Dopexamine was administered at a fixed low dose of 0.5 µg/kg/min	Intra-op, post-op	Respiratory infection, ARDS, pulmonary oedema	Low risk
Ackland 2015	n=204, UK, multi- centre	Pulse contour analysis. 1ml/kg Hartmann's + gelatin colloid until SV <10%. Dobutamine 1-20mcg/kg/min if oxygen delivery < per-op value	Intra-op, post-op	PPC	Low risk

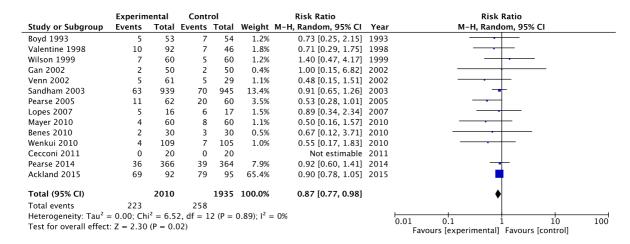


Figure 10.5. Forest plot comparing proportions of patients developing PPCs in RCTs goal directed haemodynamic therapy.

	Expe	rimer	ıtal	C	ontrol		Mean Difference			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Boyd 1993	12.5	10	51	12	9.5	53	4.3%	0.50 [-3.25, 4.25]	1993	+
Valentine 1998	13	2	60	13	2	60	16.9%	0.00 [-0.72, 0.72]	1998	•
Venn 2002	14.2	5.9	61	18.7	8.2	29	5.2%	-4.50 [-7.83, -1.17]	2002	-
Sandham 2003	10.7	5.9	997	10.7	5.9	997	17.9%	0.00 [-0.52, 0.52]	2003	•
Pearse 2005	17.5	20.8	62	29.5	34.8	60	0.7%	-12.00 [-22.21, -1.79]	2005	
Lopes 2007	7.1	1.8	17	14.8	9.7	16	2.9%	-7.70 [-12.53, -2.87]	2007	-
Mayer 2010	9.5	2.7	60	11.5	4.6	60	13.2%	-2.00 [-3.35, -0.65]	2010	•
Benes 2010	15	4.3	30	19	7	30	6.2%	-4.00 [-6.94, -1.06]	2010	-
Cecconi 2011	10	0.7	20	10	1.5	20	16.9%	0.00 [-0.73, 0.73]	2011	•
Pearse 2014	10.4	5.2	366	11.7	7.4	364	15.8%	-1.30 [-2.23, -0.37]	2014	•
Total (95% CI)			1724			1689	100.0%	-1.24 [-2.13, -0.35]		
Heterogeneity: Tau ² =	= 1.09; 0	Chi² =	39.20,	df = 9	(P < 0	.0001);	$I^2=77\%$			-100 -50 0 50 100
Test for overall effect	: Z = 2.7	73 (P =	= 0.006)						Favours [experimental] Favours [control]

Figure 10.6. Forest plot comparing hospital length of stay in RCTs of goal directed haemodynamic therapy.

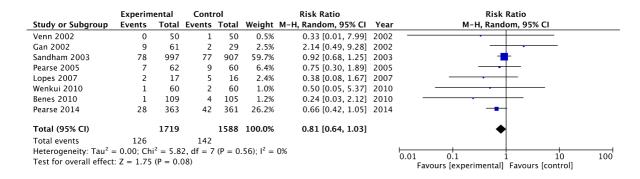


Figure 10.7. Forest plot comparing mortality in RCTs of goal directed haemodynamic therapy.

	Experim	ental	Conti	rol		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI	
Gan 2002	3	50	5	50	8.4%	0.60 [0.15, 2.38]	2002		
Venn 2002	5	60	5	30	11.9%	0.50 [0.16, 1.59]	2002		
Lopes 2007	6	16	14	17	35.6%	0.46 [0.23, 0.89]	2007		
Wenkui 2010	4	105	11	109	12.9%	0.38 [0.12, 1.15]	2010		
Benes 2010	9	60	18	60	31.2%	0.50 [0.24, 1.02]	2010	-	
Total (95% CI)		291		266	100.0%	0.47 [0.32, 0.71]		•	
Total events	27		53						
Heterogeneity: Tau2 =	= 0.00; Ch	$i^2 = 0.3$	2, df = 4	(P = 0)	.99); $I^2 = 0$	0%		0.01 0.1 1 10	100
Test for overall effect	: Z = 3.67	(P = 0.6)	0002)					0.01 0.1 1 10 Favours [experimental] Favours [control]	100

Figure 10.8. Subgroup analysis of proportions of patients developing PPCs in RCTs of goal directed fluid therapy (i.e. vasopressor and inotropic intervention trials excluded).

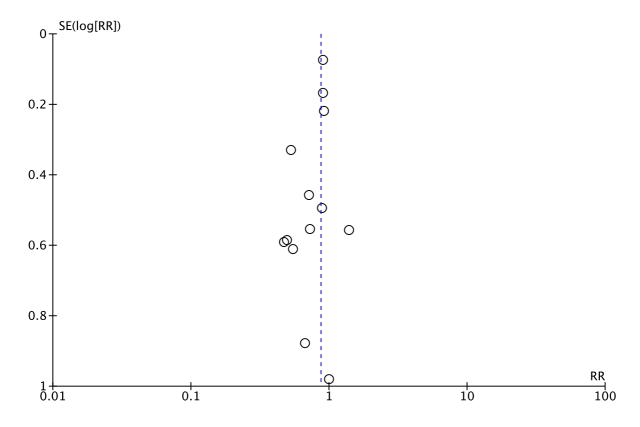


Figure 10.8 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of goal directed haemodynamic therapy.

11. Miscellaneous

Study Author and	Study Sample and		Timing of Intervention	Pulmonary	
Year	Country	Intervention description	Delivery	Outcomes	Risk of bias
Amar 2015	n=137, USA, single centre	Atorvastatin 40mg daily, 1 week before and one week after surgery	Pre-operative	Respiratory infection, respiratory failure	High risk
Berg 1997	n=691, Denmark, multi-centre	Atracurium (0.4-0.5mg/kg with 5-10mg boluses) and vecuronium (0.08-0.1 mg/kg with 1-2mg boluses)	Intra-operative, postoperative	Composite PPC	High risk
de la Gala 2017	n=174, Spain, single centre	Propofol total intravenous anaesthesia. Dose titrated to achieve BIS 40-60	Intra-operative	Composite PPC, respiratory infection, respiratory failure, atelectasis	Low risk
Parker 2015	n=322, UK, single centre	Spinal anaesthesia. Exact technique and doses of drugs used for the different types of anaesthesia was the choice of the anaesthetist.	Intra-operative	Respiratory infection	High risk
Tyagi 2010	n=100, India, single centre	Filter aseptically connected between ETT and breathing system	Intra-operative	Respiratory infection	High risk
Gaitini 2004	n=150, Israel, single centre	Proseal laryngeal mask airway or Laryngeal Tube Suction device placed after GA and neuromuscular blocking drug administration	Intra-operative	Respiratory infection (Aspiration)	Some concerns
Lai 2017	n=40, Taiwan, single centre	Igel vs ETT for laparoscopic surgery with Trendelenburg position	Intra-operative	Respiratory infection (Aspiration)	Low risk
Wong 2007	n=103, UK, single centre	Both groups were warmed during surgery, but patients in the warming group were additionally warmed 2 h before and after surgery using a conductive carbon polymer mattress	Intra-operative	Respiratory infection	Low risk
Monsel 2016	n=109, France, single centre	Spherical vs tapered shape cuffs on endotracheal tubes	Intra-operative	Respiratory infection	Low risk
Brueckmann 2015	n=150, USA, single centre	Reversal of neuromuscular blockade with Sugammadex (2 or 4 mg/kg) or usual care (neostigmine/glycopyrrolate)	Intra-operative	Respiratory infection	Low risk

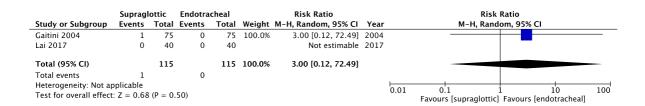


Figure 11.1. Forest plot comparing proportions of patients developing PPCs in RCTs supraglottic airway devices vs. endotracheal tube intubation.

Appendix 3. Subgroup analysis by surgical type

Incentive spirometry

Type of surgery	Number of	Number of	Risk ratio of PPC (95% CI)
	RCTs	patients	
Thoracic	2	247	0.87 (0.46 to 1.67; $p = 0.68$; $I^2 = 0\%$)
Upper GI	2	361	1.19 (0.48 to 2.97; $p = 0.71$; $I^2 = 30\%$)
Lower GI	2	1332	1.09 (0.84 to 1.40; $p = 0.53$; $I^2 = 0\%$)

Table 1. PPC risk ratios for incentive spirometry, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Supervised physiotherapy

Type of surgery	Number of	Number of	Risk ratio of PPC (95% CI)
	RCTs	patients	
Thoracic	3	279	0.91 (0.34 to 2.41; $p = 0.85$; $I^2 = 60\%$)
Upper GI	4	581	0.43 (0.17 to 1.08; $p = 0.07$; $I^2 = 65\%$)
Lower GI	3	426	0.53 (0.21 to 1.34; $p = 0.18$; $I^2 = 25\%$)

Table 2. PPC risk ratios for physiotherapy, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Drug therapies to improve pulmonary function

Type of surgery	Number of	Number of	Risk ratio of PPC (95% CI)

	RCTs	patients	
Thoracic	2	200	0.30 (0.11 to 0.77; $p = 0.01$; $I^2 = 0\%$)
Upper GI	1	252	0.45 (0.24 to 0.85; p = 0.01; $I^2 = N/A$)
Lower GI	0	0	N/A

Table 3. PPC risk ratios for of prophylactic mucolytics, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Intraoperative anaesthetic gas composition

Type of surgery	Number of RCTs	Number of patients	Risk ratio of PPC (95% CI)
Thoracic	0	0	N/A
Upper GI	0	0	N/A
Lower GI	2	1416	1.12 (0.80 to 1.58; $p = 51$; $I^2 = 0\%$)

Table 4. PPC risk ratios for of FiO2 0.8 versus 0.3, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Intraoperative ventilation strategies

Type of surgery	Number of RCTs	Number of patients	Risk ratio of PPC (95% CI)
Thoracic	1	100	0.18 (0.04 to 0.78; $p = 0.02$; $I^2 = N/A$)
Upper GI	0	0	N/A
Lower GI	3	1347	0.61 (0.32 to 1.18; $p = 0.14$; $I^2 = 89\%$)

Table 5. PPC risk ratios for of lung protective ventilation, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Prophylactic non-invasive ventilation

Type of surgery	Number of RCTs	Number of patients	Risk ratio of PPC (95% CI)
Thoracic	3	442	1.00 (0.70 to 1.43; $p = 1.00$; $I^2 = 14\%$)
Upper GI	3	147	0.35 (0.16 to 0.79; $p = 0.01$; $I^2 = 0\%$)
Lower GI	0	0	N/A

Table 6. PPC risk ratios for prophylactic non-invasive ventilation (bilevel and CPAP), stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Analgesia

Type of surgery	Number of	Number of	Risk ratio of PPC (95% CI)
	RCTs	patients	
Thoracic	1	50	0.75 (0.19 to 3.01; $p = 0.69$; $I^2 = N/A$)
Upper GI	0	0	N/A
Lower GI	7	2216	0.74 (0.62 to 0.89; $p = 0.001$; $I^2 = 0\%$)

Table 7. PPC risk ratios for epidural, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Lifestyle modifications

Type of surgery	Number of RCTs	Number of patients	Risk ratio of PPC (95% CI)
Thoracic	0	0	N/A
Upper GI	0	0	N/A
Lower GI	3	463	0.89 (0.27 to 2.93; $p = 0.85$; $I^2 = 0\%$)

Table 8. PPC risk ratios for incentive spirometry, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Enhanced post-operative recovery pathways

Type of surgery	Number of	Number of	Risk ratio of PPC (95% CI)
	RCTs	patients	
Thoracic	1	60	0.29 (0.12 to 0.69; $p = 0.005$; $I^2 = N/A$)
Upper GI	0	0	N/A
Lower GI	3	399	0.38 (0.20 to 0.71; $p = 0.003$; $I^2 = 0\%$)

Table 9. PPC risk ratios for enhanced recovery after surgery, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Goal directed haemodynamic and fluid therapy

Type of surgery	Number of	Number of	Risk ratio of PPC (95% CI)
	RCTs	patients	
Thoracic	0	0	N/A

Upper GI	0	0	N/A
Lower GI	7	726	0.56 (0.21 to 1.46; $p = 0.23$; $I^2 = 30\%$)

Table 10. PPC risk ratios for restrictive vs. liberal fluid administration, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Type of surgery	Number of	Number of	Risk ratio of PPC (95% CI)
	RCTs	patients	
Thoracic	0	0	N/A
Upper GI	0	0	N/A
Lower GI	10	3555	0.89 (0.79 to 1.01; $p = 0.08$; $I^2 = 0\%$)

Table 11. PPC risk ratios for perioperative goal directed haemodynamic therapy, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Appendix 4. Trial sequential analysis

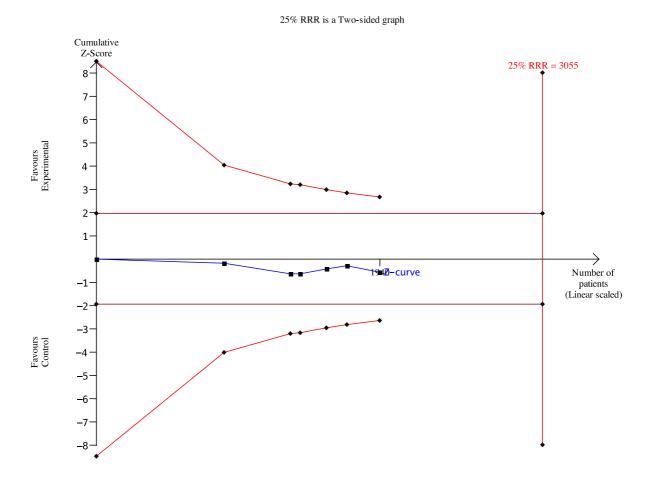


Figure 1. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing incentive spirometry (IS) to control. The upper half of the graph above the zero axis represents the area of advantage with IS and the lower half represents the advantage area with control. The green lines at +1.96 and -1.96 on the Y-axis represent the conventional model boundaries for TSA with an α of 5%. The vertical red line shows the calculated minimum required information size (IS) for the conventional boundary model for making conclusions is 3055. The symmetrical red curves represent the calculated trial sequential monitoring boundaries (TSMBs). The blue line represents the cumulative z-value, with each consecutive trial marked by a filled square. Firm evidence has been reached when the cumulative z-curve crosses the calculated boundaries before the calculated IS. Spurious significant differences between treatments are found when the cumulative z-curve crosses the traditional z = -1.96 or z = 1.96, but not the calculated TSMBs. The cumulative z-score line (blue) does not crosses the conventional boundaries (green lines) indicating there is no conclusive evidence of superiority for the IS or control groups based upon a 25% relative risk reduction.

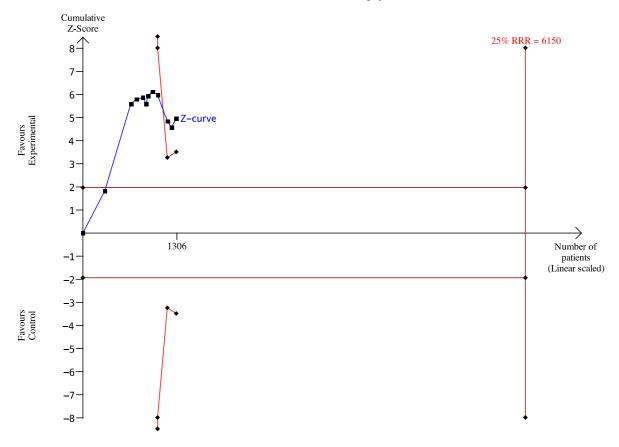


Figure 2. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing supervised physiotherapy to control. The cumulative z-curve crosses both the conventional boundaries and calculated trial sequential monitoring boundaries (TSMBs). This result indicates there is firm evidence of superiority for the supervised physiotherapy (based on a 25% relative risk reduction). Although the calculated IS needed (6,150 participants) has not been reached yet (1,306 participants so far), no more additional participants are needed because the cumulative z-curve crosses the TSMB.

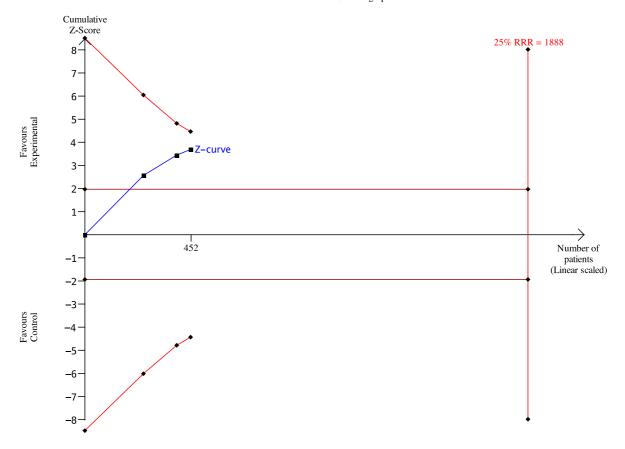


Figure 3. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing Ambroxol to control. The cumulative z-curve crosses the conventional boundaries but not the calculated trial sequential monitoring boundaries (TSMBs). Nor has the calculated IS needed been reached. This result indicates that conventional meta-analysis may have produced a potential spurious positive result (type 1 error) for Ambroxol (based on a 25% relative risk reduction).

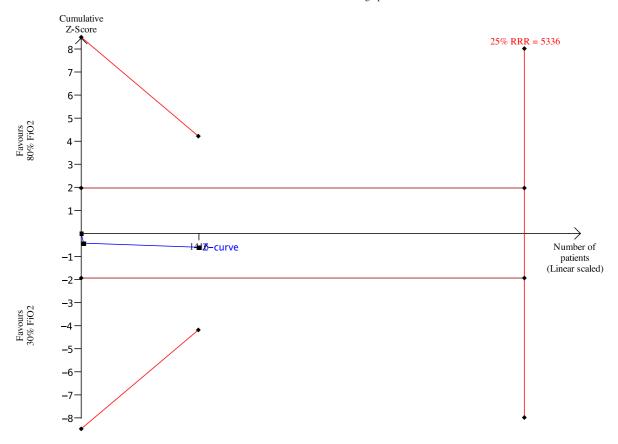


Figure 4. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing FiO2 0.8 to FiO2 0.3. The cumulative z-curve does not cross the conventional or the trial sequential monitoring boundaries (TSMBs). The actual information size (1416) is far short of the calculated IS needed (5336), based on a 25% relative risk reduction. This result is inconclusive for either FiO2 0.3 or 0.8 in preventing PPCs.

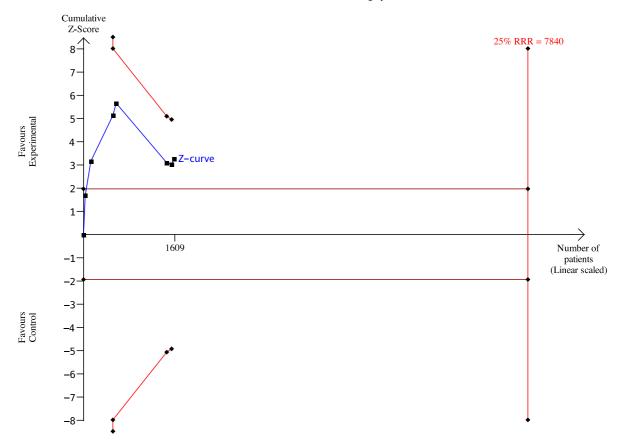


Figure 5. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing lung protective ventilation to control. The cumulative z-curve crosses the conventional boundaries but not the calculated trial sequential monitoring boundaries (TSMBs). Nor has the calculated IS needed been reached. This result indicates that conventional meta-analysis may have produced a potential spurious positive result (type 1 error) for lung protective ventilation (based on a 25% relative risk reduction).

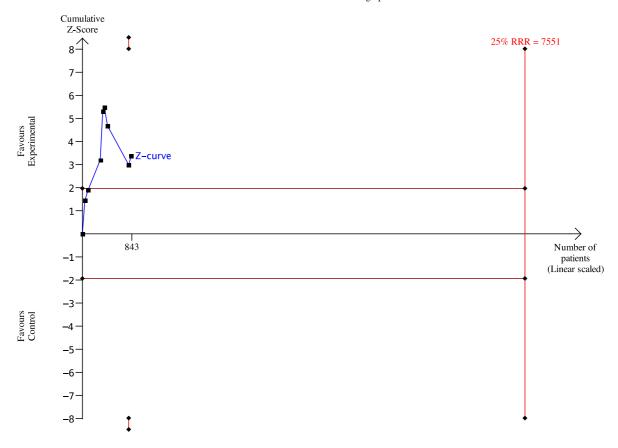


Figure 6. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing continuous positive airway pressure (CPAP) to control. The cumulative z-curve crosses the conventional boundaries but not the calculated trial sequential monitoring boundaries (TSMBs). Nor has the calculated IS needed been reached. This result indicates that conventional meta-analysis may have produced a potential spurious positive result (type 1 error) for CPAP (based on a 25% relative risk reduction).

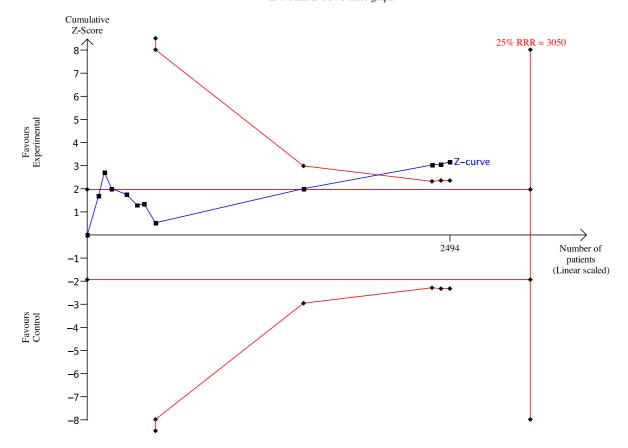


Figure 7. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing epidural analgesia to control. The cumulative z-curve crosses both the conventional boundaries and calculated trial sequential monitoring boundaries (TSMBs). This result indicates there is firm evidence of superiority for epidural analgesia (based on a 25% relative risk reduction). Although the calculated IS needed (3,050 participants) has not quite been reached yet (2,494 participants so far), no more additional participants are needed because the cumulative z-curve crosses the TSMB.

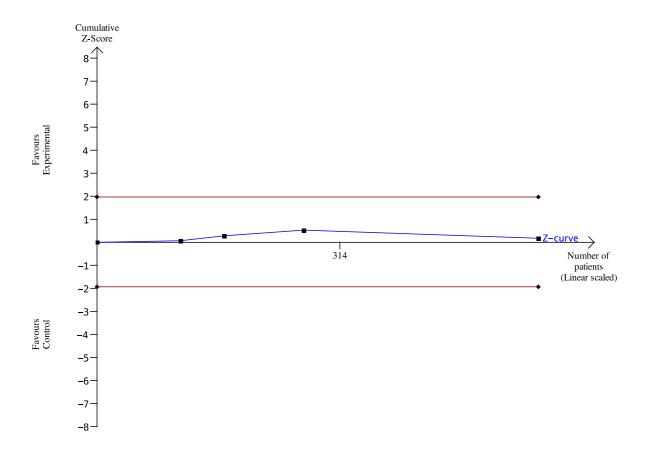


Figure 8. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing smoking cessation therapies to control. This result is inconclusive for whether smoking cessation therapies prevent PPCs.

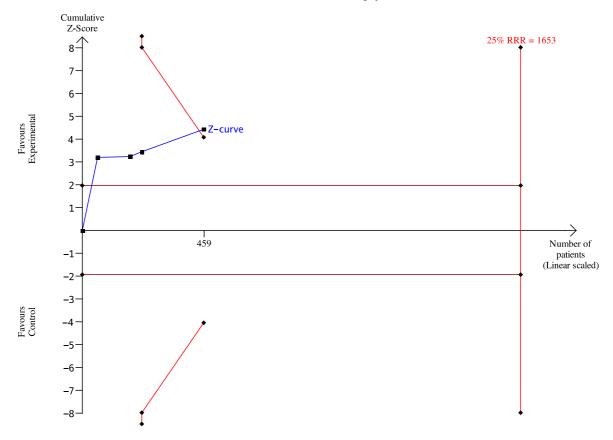


Figure 9. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing enhanced recovery after surgery (ERAS) protocols to control. This result indicates there is firm evidence of superiority for ERAS (based on a 25% relative risk reduction).

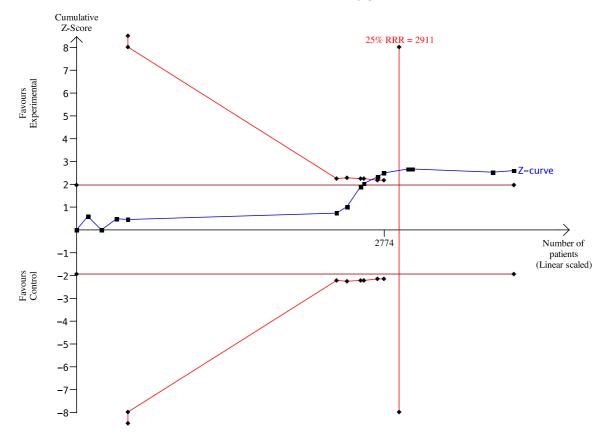


Figure 10. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing goal directed haemodynamic therapies to control. The cumulative z-curve crosses both the conventional boundaries and calculated trial sequential monitoring boundaries (TSMBs). This result indicates there is conclusive evidence of superiority for the goal directed haemodynamic therapies (based on a 25% relative risk reduction). The required information size was exceeded, hence minimising the chance of both type I and II errors.

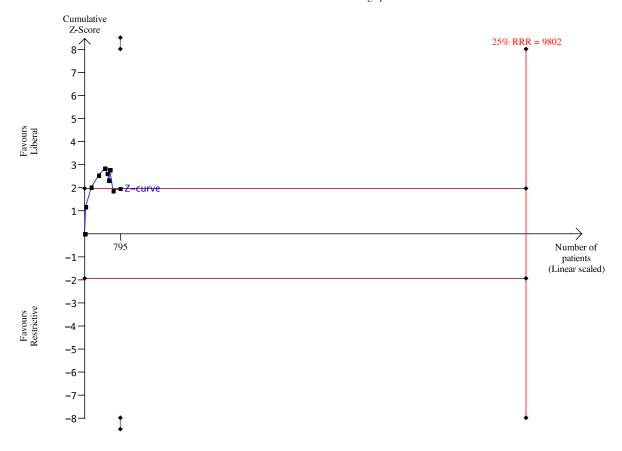


Figure 11. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing restrictive (intervention) fluid therapies to liberal (control) fluid therapy. The cumulative z-curve is on the margins of the conventional boundaries but is far from the calculated trial sequential monitoring boundaries (TSMBs). The actual IS is far from the calculated IS needed to demonstrate a 25% relative risk reduction. This result indicates that far more trials are needed to produce firm evidence, although a smaller number of trials with a similar outcome may result in the conventional boundaries being crossed and a potentially spurious positive result produced by conventional meta-analysis.