

**TABLE 1** Characteristics of the included studies (MISA group vs. control group).

Study ID	Patient population	Type and  dose of  surfactant	Mean/median  GA ( W )  Mean/median BW ( g )	Intervention vs.  control sample size	AS n(%);  CS n(%);  Apgar 5 min.	Criteria for surfactant	Criteria for rescue  intubation
Göpel et al <sup>14</sup> ,  2011  ISRCTN05025922	26 ~ 28 <sup>6/7</sup> W  BW < 1.5 kg  German  12 NICUs  2007 ~ 2010 <sup>a</sup>	Curosurf,  100 mg/kg	GA: 27.6 ± 0.8 vs. 27.5 ±  0.8 W;  BW: 975 ± 244 vs. 938 ±  205 g	LISA vs.  Endotracheal  instillation  220 ( 108 vs. 112 )	AS: 107 ( 96% ) vs. 104 ( 96% );  CS: 101 ( 94% ) vs. 104 ( 93% )	NCPAP ( ≥ 4 cmH <sub>2</sub> O) with  FiO <sub>2</sub> > 0.3 for LISA group  and intubation with FiO <sub>2</sub> ( 0.3-0.6 ) for control group  within 12 h of life	FiO <sub>2</sub> ( 0.3~ 0.6 );  Or PH ( 7.15 -7.2 );  Or PCO <sub>2</sub> ( 60 ~70 mmHg ).
Heidarzadeh et al <sup>15</sup> ,  2013	< 32 W  Iran  Single NICU	Curosurf;  200 mg/kg	GA: 30.08 ± 1.5 vs. 29.6 ± 2.5 W;  BW: 1489.7 ± 76.6 vs.	TEC vs. INSURE  80 ( 38 vs. 42 )	AS: 28 ( 74%) vs. 31 ( 74% );  CS: 23 ( 61% ) vs. 31 ( 74% );  Apgar: both groups were >6	NCPAP with FiO <sub>2</sub> ≥ 30% to  maintain SpO <sub>2</sub> > 85%	

	2010 ~ 2012		1383.3 ± 58.3 g				
Kanmaz et al <sup>16</sup> ,	< 32W	Curosurf;	GA: 28 ± 2 vs. 28.3 ± 2	LISA vs. INSURE	AS: 73 ( 73% ) vs. 81 ( 81%);	NCPAP (5~7 cmH <sub>2</sub> O) with	CPAP(> 7 cmH <sub>2</sub> O) with
2013	Turkey	100 mg/kg	W;	200 ( 100 vs. 100 )	CS: 75 ( 75% ) vs. 83 ( 83%);	FiO <sub>2</sub> ≥ 0.4 to maintain SpO <sub>2</sub>	FiO <sub>2</sub> ≥ 0.6;
NCT01329432	Single NICU		BW: 1093 ± 270 vs. 1121		Apgar: 7 ( 5-9 ) vs. 7 ( 6-9 ) <sup>b</sup>	( 85-92% ) within 2 h of life	Or PH < 7.2.
	2010 ~ 2011		± 270 g				
Mirnia et al <sup>17</sup> ,	27 ~ 32 <sup>6/7</sup> W	Curosurf;	GA: 29.6±1.7 vs.	LISA vs. INSURE	AS: 44 ( 66.7% ) vs. 44 (	NCPAP( 5~6 cmH <sub>2</sub> O) with	PCO <sub>2</sub> > 50 ~60 mmHg and
2013	Iran	200 mg/kg	29.6±1.7 W;	136 (66 vs. 70)	62.9% ) ;	FiO <sub>2</sub> ≥ 0.3 to maintain SpO <sub>2</sub>	PH < 7.2.
	3 NICUs		BW: 1339.3±406 vs.		CS: 48 ( 72.7% ) vs. 49 ( 70%	> 85%.	
	2010 ~ 2012		1304±331 g		) ;		
					Apgar: ≥4 ( 8 vs. 7 ) <sup>c</sup>		
Bao et al <sup>18</sup> ,	28 ~ 32 <sup>6/7</sup> W	Curosurf;	GA: 29.1 ± 1.5 vs. 29.3 ±	LISA vs. INSURE	AS: 42 ( 89.4% ) vs. 40 (	NCPAP ( ≥ 7 cmH <sub>2</sub> O) with	FiO <sub>2</sub> ≥ 0.5;
2015	China	200 mg/kg	1.6 W;	90 (47 vs. 43)	93%);	FiO <sub>2</sub> ≥ 0.3 ( 28-29 W ) ;	Or PH < 7.2;
ChiCTR-ICR-	Single center		BW: 1034 ± 221 vs. 1087		CS: 35 ( 74.5% ) vs. 33 (	Or FiO <sub>2</sub> ≥ 0.35 ( 30-32 W)	Or significant apnea.

15006001	2012		± 198 g		76.7%);	to maintain SpO <sub>2</sub> ( 85-	
					Apgar: 8.7 ± 0.6 vs. 8.8 ± 0.7.	95% ) within 2 h of life.	
Kribs et al <sup>19</sup> ,	23 ~ 26 <sup>6/7</sup> W	Curosurf;	GA: 25.3 ± 1.1 vs. 25.2 ±	LISA vs.	AS: 105 ( 98.1% ) vs. 102 (	NCPAP with FiO <sub>2</sub> ≥ 0.3 to	FiO <sub>2</sub> > 0.45 for more than
2015	German	100 mg/kg	0.91 W;	Endotracheal	98.1%);	maintain SpO <sub>2</sub> > 83%;	2h during CPAP to obtain
ISRCTN64011614	13 NICUs		BW: 711 ± 195 vs. 674 ±	instillation	CS: 94 ( 87.8% ) vs. 96 (	Or silverman score ≥ 5.	PO <sub>2</sub> > 45 mmHg;
	2009 ~ 2012		165 g	211 (107 vs. 104)	92.3% );		Or PH < 7.15;
					Apgar: 8 ( 7-9 ) vs. 8 ( 8-9 ) <sup>d</sup>		Or severe apnea.
Mohammadizadeh	≤ 34 W	Curosurf;	GA: 30 ± 2 vs. 31 ± 2 W;	LISA vs. INSURE	AS: 17 ( 89.5% ) vs. 15 (	NCPAP ( 6 cmH <sub>2</sub> O) with	FIO <sub>2</sub> ≥ 70% for more than
et al <sup>20</sup> ,	1000 ~ 1400g	200 mg/kg	BW: 1289 ± 219 vs. 1428	38 ( 19 vs. 19 )	84.2% );	FiO <sub>2</sub> ≥ 0.3 to maintain SpO <sub>2</sub>	2 h or ≥ 40% for more than
2015	Iran		± 272 g		CS: 19 ( 100% ) vs. 17 (	( 87-92%);	12 h to maintain SpO <sub>2</sub> ≥
392176	2 NICU				89.5% );	Or Silverman score ≥ 5	87%;
	2012 ~ 2013				Apgar: both groups were ≥ 4	within 4 h of life.	Or pH < 7.2 or PaCO <sub>2</sub> > 65

							mmHg;
							Or occurrence of one major
							apnea or six minor apnea
							within 6 h.
Mosayebi et al <sup>21</sup> ,	28 ~ 34 <sup>6/7</sup> W	Curosurf;	GA: 31.9 ± 1.5 vs. 32.6 ±	MIST vs. INSURE	AS: 15 ( 51.9% ) vs. 14 (	NCPAP (5~8 cmH <sub>2</sub> O) with	FiO <sub>2</sub> > 0.5 and pH < 7.2;
2017	Iran	200 mg/kg	1.1 W;	53 ( 27 vs. 26 )	57.7% );	FiO <sub>2</sub> ≥ 0.4 to maintain SpO <sub>2</sub>	Or prolonged apnea.
IRCT2014080716	Single center		BW: 1910.0 ± 433.0 vs.		CS: 24 ( 92.3% ) vs. 25 (	(85-92%) within 2 h of life.	
937N4	2013 ~ 2014		1791.9 ± 554.3 g		92.6% ) ;		
					Apgar: ≥ 4 ( 8.2 ( 4-10 ) vs.		
					8.3 ( 7-10 ) <sup>b</sup> )		
Halim et al <sup>22</sup> ,	≤ 34 W	Survanta,	BW: 1300 ( 600 ) vs.	LISA vs. INSURE	AS: 38 ( 76% ) vs. 30 ( 60%	NCPAP( 5~7 cmH <sub>2</sub> O) with	FiO <sub>2</sub> > 0.4;
2019	Pakistan	100 mg/kg	1400 ( 400 ) g <sup>d</sup> ;	100 (50 vs. 50)	);	FiO <sub>2</sub> ≥ 0.3 to maintain SpO <sub>2</sub>	Or severe work of
	Single center				CS: 38 ( 76% ) vs. 30 ( 60% );	( 88-92%) within 12 h of	breathing;

	2017					life.	Or persistent apneas.
Jena et al <sup>23</sup> ,	≤ 34 W	Neosurf,	GA: 31 ( 29-33 ) vs. 31 (	LISA and MIST vs.	AS: 106 ( 61% ) vs. 111 (	NCPAP ( 6 cmH <sub>2</sub> O) with	CPAP(> 7 cmH <sub>2</sub> O) and
2019	India	135 mg/kg	29-33 ) W <sup>d</sup> ,	INSURE	63% );	FiO <sub>2</sub> ≥ 0.3 to maintain SpO <sub>2</sub>	FiO <sub>2</sub> > 0.7;
	3 NICUs		BW: 1630 ( 1217-2058 )	350 ( 175 vs. 175 )	CS: 105 ( 60% ) vs. 120 (	( 90-95%) within 6 h of life.	Or PH < 7.2 or/and PCO <sub>2</sub> >
	2013 ~ 2017		vs. 1683 ( 1316-2041 ) g <sup>d</sup>		69% );		60mmHg;
					Apgar: 9 ( 8-9 ) vs. 9 ( 8-9 ) <sup>d</sup>		Or recurrent apnea.
Gupta et al <sup>24</sup> ,	28 ~ 34 W	Curosurf;	GA: 30.07 ± 1.5 vs. 29.90	MIST vs. INSURE	AS: 23 ( 79.3%) vs. 24 (	NIPPV (PIP ( 12-15	PH < 7.2 and PCO <sub>2</sub> >
2020	India	200 mg/kg	± 1.67 W;	58 ( 29 vs. 29 )	82.8%);	cmH <sub>2</sub> O), PEEP ( 5-6	60mmHg;
CTRI/	Single center		BW: 1225 ± 281 vs. 1222		CS: 19 ( 65.5%) vs. 16 (	cmH <sub>2</sub> O)) with FiO <sub>2</sub> > 30%	Or recurrent apnoea;
2019/03/017992	2019		± 322 g		55.2%);	to maintain SpO <sub>2</sub> ( 90-	Or requiring NIPPV setting
					Apgar: 8 ( 7-9 ) vs. 8 ( 7-9 ) <sup>d</sup>	95%) within 6 h of life.	of FiO <sub>2</sub> > 60%, PIP > 25
							cmH <sub>2</sub> O and PEEP> 6

cmH<sub>2</sub>O.

Han et al <sup>25</sup> ,	< 32 W	calf	GA: 30.6 ± 1.6 vs. 30.8 ±	LISA and MIST vs.	AS: 110 ( 72.9%) vs. 114 (	NCPAP ( 6~8 cmH <sub>2</sub> O) with	Respiratory distress
2020	China	pulmonary	1.3 W;	INSURE	77.6%);	FiO <sub>2</sub> ≥0.4 to maintain SpO <sub>2</sub>	progressively developed
NCT04077333	8 NICUs	surfactant,	BW: 1427.6 ± 290.2 vs.	298 ( 151 vs. 147 )	CS: 101 ( 66.9%) vs. 112 (	> 85% within 6 h of life.	and NCPAP failure.
	2017 ~ 2018.	70~100 mg/kg	1418.7 ± 273.0 g		76.2%) ;		
					Apgar: 9.3 ± 1.3 vs. 9.2 ± 1.5		
Yang et al <sup>26</sup> ,	32 ~ 36 <sup>6/7</sup> W	Curosurf;	GA: 33.7 ± 1.0 vs. 34.1 ±	LISA vs. INSURE	AS: 13 ( 27.7% ) vs. 11 ( 22%	NCPAP (> 6 cmH <sub>2</sub> O) with	FiO <sub>2</sub> ≥ 0.6, pH < 7.20
2020	China	200 mg/kg	1.3 W;	97 (47 vs. 50)	);	FiO <sub>2</sub> > 40% to maintain	and/or PaCO <sub>2</sub> > 65 mmHg;
	Single center		BW: 2106 ± 315 vs. 2219		CS: 19 ( 40.4% ) vs. 22 (	SpO <sub>2</sub> ( 89-95%) within 12 h	Or severe apnea occurred.
	2017 ~ 2018		± 314 g		44.0% );	of life.	
					Apgar: 8.4 ± 0.7 vs. 8.6 ± 0.6.		

Abbreviations: AS, antenatal steroids; BW, birth weight; CS, caesarean section; FiO<sub>2</sub>, fractional inspired oxygen; GA, gestational age; INSURE: intubation, surfactant administration and

extubation; LISA, less invasive surfactant administration; MIST, minimally invasive surfactant therapy; NCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; PEEP, positive end-expiratory preassure; PIP, peak inspiratory pressure; SpO<sub>2</sub>, pulse oxygen saturation; TEC, thin endotracheal catheter.

<sup>a</sup> Enrollment years

<sup>b</sup> Data are median(min,max)

<sup>c</sup> Data are median

<sup>d</sup> Data are median(IQR)

**TABLE2** Risk of bias assessment for all included studies

Study	Random sequence generation	Allocation concealment	Binding of participants and personnel	Binding of outcome data	Incomplete outcome data	Selective reporting	Other bias	Overall
Göpel et al <sup>14</sup>	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Unclear risk <sup>a</sup>	Low risk
Heidarzadeh et al <sup>15</sup>	Unclear risk	Low risk	High risk	High risk	High risk <sup>b</sup>	Unclear risk <sup>c</sup>	Low risk	Moderate risk
Kanmaz et al <sup>16</sup>	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk
Mirnia et al <sup>17</sup>	Unclear risk	Unclear risk	High risk	High risk	Low risk	Unclear risk <sup>c</sup>	Low risk	Moderate risk
Bao et al <sup>18</sup>	Low risk	Unclear risk	High risk	High risk	Low risk	Unclear risk <sup>d</sup>	Unclear risk	Moderate risk
Kribs et al <sup>19</sup>	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk
Mohammadizadeh et al <sup>20</sup>	Low risk	Low risk	High risk	High risk	Low risk	High risk <sup>e</sup>	Low risk	Low risk
Mosayebi et al <sup>21</sup>	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk
Halim et al <sup>22</sup>	Low risk	Low risk	High risk	High risk	Low risk	Unclear risk <sup>c</sup>	Low risk	Low risk
Jena et al <sup>23</sup>	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk



Gupta et al <sup>24</sup>	Low risk	Low risk	High risk	High risk	Low risk	High risk <sup>d</sup>	Low risk	Low risk
Han et al <sup>25</sup>	Low risk	Low risk	High risk	High risk	Low risk	High risk <sup>f</sup>	Low risk	Low risk
Yang et al <sup>26</sup>	Low risk	Low risk	High risk	High risk	Low risk	Unclear risk <sup>e</sup>	Low risk	Low risk

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<sup>a</sup> Not all infants in both groups received surfactants.

<sup>b</sup> No withdrawal information reported.

<sup>c</sup> Trials were not registered in the registry.

<sup>d</sup> The end date of the trial was earlier than the registration date.

<sup>e</sup> No data was provided on some major neonatal complications, such as necrotizing enterocolitis (NEC), pneumothorax and retinopathy of prematurity (ROP).

<sup>f</sup> Some infants who had intubated ventilation support within 72 h of life were excluded after randomisation.

**TABLE 3** Neonatal outcomes

Outcomes	Included studies	MISA group positive/total	Control group positive/total	FEM/REM	Heterogeneity(I <sup>2</sup> )	RR(95% CI)	p
All-cause mortality	10 <sup>14-23</sup>	67/737	90/741	FEM	8%	0.75 [0.56 to 1.00]	0.05
BPD at 36 weeks	12 <sup>14-21, 23-26</sup>	89/914	150/917	FEM	3%	0.59 [0.46 to 0.75]	< 0.0001
MV within 72 h of life	8 <sup>14, 16-18, 20, 21, 24, 26</sup>	89/443	151/449	FEM	36%	0.60 [0.48 to 0.75]	< 0.00001
MV during hospitalization	8 <sup>14-17, 19, 21-23</sup>	227/671	360/679	REM	72%	0.64 [0.49 to 0.82]	0.0005
Pneumothorax	9 <sup>14-19, 21, 22, 26</sup>	29/590	49/597	FEM	0%	0.60 [0.39 to 0.93]	0.02
Pulmonary hemorrhage	6 <sup>14, 16, 19, 21, 22, 25</sup>	16/543	24/539	FEM	0%	0.67 [0.36 to 1.23]	0.19
hsPDA	11 <sup>14-19, 21-25</sup>	239/898	266/898	FEM	14%	0.88 [0.78 to 1.00]	0.04
Definite NEC	8 <sup>14-17, 19, 21, 23, 26</sup>	29/668	46/679	FEM	28%	0.65 [0.42 to 1.00]	0.05
ROP ( > stage II or need for treatment)	7 <sup>14-17, 19, 21, 25</sup>	23/691	32/694	FEM	0%	0.73 [0.44 to 1.22]	0.23
IVH (any grades)	11 <sup>14-22, 24, 25</sup>	123/914	125/917	FEM	7%	0.97 [0.78 to 1.20]	0.76

Severe IVH (grade III or higher)	8 <sup>14-16, 18, 19, 21, 24, 25</sup>	44/654	59/653	FEM	0%	0.75 [0.52 to 1.08]	0.12
PVL	4 <sup>14, 18, 19, 25</sup>	17/413	18/406	FEM	45%	0.93 [0.49 to 1.77]	0.82
Surfactant reflux	5 <sup>16-18, 21, 26</sup>	54/287	25/289	FEM	0%	2.12 [1.37 to 3.29]	0.0008
Need for additional surfactant	11 <sup>15-22, 24-26</sup>	141/829	121/829	FEM	0%	1.17 [0.95 to 1.45]	0.15

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Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; Definite NEC, definite necrotizing enterocolitis, i.e. NEC  $\geq$  stage 2; FEM, fixed effect model; hsPDA, haemodynamically significant patent ductus arteriosus; IVH, intraventricular haemorrhage; MISA, minimally invasive surfactant administration; MV, mechanical ventilation; PVL, periventricular leukomalacia; REM, random effect model; ROP, retinopathy of prematurity; RR, risk ratio.