Table 3. Clinical trials of the use of iNO in pediatric surgery

CITATION	STUDY DESIGN	N	SETTING	COMPARISON	MEASURES	PRIMARY RESULTS	SAFETY
Goldman AP et al. [41]	Randomized, crossover	13	congenital	INO (20ppm) vs prostacyclin	pulmonary hemodynamics	NO and prostacyclin reduced PAP, MPAP was significantly lower with NO than with prostacyclin ($p < 0.05$). Mean pulmonary to systemic arterial pressure ratio was significantly lower with NO than prostacyclin (0.46 -+ 0.04 vs 0.68 + 0.05; $p < 0.01$). iNO was a more effective and selective pulmonary vasodilator than prostacyclin	Four patients died. One died of acute PH after iNO discontinuation and before iNO could be restarted. 3 died of underlying lung disease, multi-organ failure and left ventricular failure due to severe left ventricular hypoplasia respectively. No related toxicity was noted during iNO except in 1 patient where metHB levels rose transiently to 8%. NO_2 concentrations ≤1.2 ppm.
Russell IA et al. [42]	Randomized, double blind	40	postop PH after congenital heart defect repair	iNO vs placebo	MPAP pulmonary and systemic hemodynamics	in infants and children undergoing congenital heart surgery, iNO selectively reduces MPAP in patients who emerge from CPB with PH and has no effect on those who emerge without it.	Inhalation of iNO vs placebo did not significantly alter systemic hemodynamics (mSAP, heart rate, atrial pressure The median metHB level was 1.6% + 0.4% in the patient group that received iNO. Adverse events were not noted
Day RW et al. [43]	Randomized	40	Congenital heart defect	iNO (20 ppm) vs conv therapy	pulmonary hemodynamics, gas exchange, # crises	No significant reduction in PH crises for iNO 20ppm compared to conventional therapy	Maximum metHB values were slightly increased in iNO group (1.4% + 0.1% versus 1.1% + 0.1%, p=0.023). No known complications or adverse events were associated with iNO
Miller O et al. [44]	Randomized, double blind	124		iNO vs placebo	# PH crises, time on study gas, and hours spent in intensive care	Vs placebo, infants receiving iNO had fewer PHTC and shorter times until meeting criteria for extubation. Time to wean infants off study gas was 35% longer with iNO than placebo (p=0.19), but total time on iNO was still 30 h shorter for (p=0.023).	The metHB level remained less than 3.4% in all and the NO_2 level was below 2.1ppm for all cases
Morris et al. [45]	Randomized, crossover	12	biventricular repair of congenital heart disease	iNO vs. hyperventilation.	CO and derived hemodynamic parameters	NO was selective for pulmonary circulation and did not increase SVR	metHB remained below 2 % in all patients. No rebound PH was seen on discontinuation of iNO No adverse events related to iNO therapy noted.

CITATION	STUDY DESIGN	N	SETTING	COMPARISON	MEASURES	PRIMARY RESULTS	SAFETY
Stocker C et al. [46]	Randomized, crossover	15	at risk for PH early after cardiac surg	iNO, sildenafil	Pulmonary hemodynamics, CO	With iNO first, iNO lowered PVRI (p=0.01); sildenafil further reduced PVRI to 2.45 units p<0.05. With sildenafil first, PVRI was reduced p<0.05 then fell to 2.15 units (p=0.01) with addition of iNO. In both groups, sildenafil reduced the systemic blood pressure and systemic VR (p<0.01) and worsened arterial oxygenation and the alveolar-arterial gradient (p<0.05).	No adverse events were noted
Khazin J et al. [47]	Randomized, double blind	40	PH and repair of CHD	iNO (30 ppm), milrinone	Pulmonary and systemic pressures, $PaCO_2$, SaO_2, and pH values were recorded before bypass, after weaning from CPB, 10 and 20 minutes after starting each regimen, and 10 minutes after cessation of treatment	Mean systemic BP was lower ($p < 0.05$) with the combined treatment after discontinuation of the drugs. Mean PAP was lower in the combined group ($p < 0.05$), no difference with regard to pH, $PaCO_2$, and PaO_2. Milrinone + NO produced a more pronounced decrease in PAP than milrinone alone	
Cai J et al. [48]	Randomized	31	marked elevation of transpulmonary pressure gradient (>10 mm Hg) or central venous pressure (CVP, >15 mm Hg) after modified fenestrated Fontan	iNO vs iNO+milrinone	Hemodynamics, arterial blood oxygenation, and occurrence of withdrawal failure/rebound	iNO and milrinone provided additive benefits as compared with exclusive use of iNO for patients with elevated PVR after Fontan procedure.	Occurrence of iNO withdrawal failure during its weaning or rebound after its discontinuation was significantly lower in group iNO + milrinone.

BP=blood pressure, CI=cardiac index, CO=cardiac output, CPB= cardiopulmonary bypass, CVP=central venous pressure, Hg=mercury, HR=heart rate, iNO=inhaled nitric oxide, i-PGi2=inhaled prostacyclin, LAP=left atrial pressure, LVAD=left ventricular assist device, MAP=mean arterial pressure, metHB=methemoglobin, MPAP=mean pulmonary arterial pressure, NO_2=nitrogen dioxide, NTP=nitroprusside, PCWP= pulmonary capillary wedge pressure, PH=pulmonary hypertension, PGE1=IV prostaglandin E1, PVR=pulmonary vascular resistance, PVRI= pulmonary vascular resistance index, RVEF=right ventricular ejection fraction, SVRI=systemic vascular resistance index