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An evidence-based review of the use of vasoactive and inotropic medications in post-operative paediatric patients after cardiac surgery with cardiopulmonary bypass from 2000 to 2020

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Abstract

Background: Infants with moderate-to-severe CHD frequently undergo cardiopulmonary bypass surgery in childhood. Morbidity and mortality are highest in those who develop post-operative low cardiac output syndrome. Vasoactive and inotropic medications are mainstays of treatment for these children, despite limited evidence supporting their use. *Methods:* To help inform clinical practice, as well as the conduct of future trials, we performed a systematic review of existing literature on inotropes and vasoactives in children after cardiac surgery using the PubMed and EMBASE databases. We included studies from 2000 to 2020, and the patient population was defined as birth – 18 years of age. Two reviewers independently reviewed studies to determine final eligibility. *Results:* The final analysis included 37 papers. Collectively, selected studies reported on 12 different vasoactive and inotropic medications in 2856 children. Overall evidence supporting the use of these drugs in children after cardiopulmonary bypass was limited. The majority of studies were small with 30/37 (81%) enrolling less than 100 patients, 29/37 (78%) were not randomised, and safety and efficacy endpoints differed widely, limiting the ability to combine data for meta-analyses. *Conclusion:* Vasoactive and inotropic support remain critical parts of post-operative care for children after cardiopulmonary bypass surgery. There is a paucity of data for the selection and dosing of vasoactives and inotropes for these patients. Despite the knowledge gaps that remain, numerous recent innovations create opportunities to rethink the conduct of clinical trials in this high-risk population.

Approximately 0.4–5% of infants are born with CHD.[1] Those with moderate-to-severe illness will undergo surgery in childhood, often requiring the use of cardiopulmonary bypass.[1] Cardiac surgery on cardiopulmonary bypass remains a high-risk operation, with an overall mortality of ~3% and major complications in up to 38% for the most complex operations.[2,3] Morbidity and mortality are highest in children who develop post-operative low cardiac output syndrome, which occurs in up to 25% of infants.[4,5] Post-operative low cardiac output syndrome may be prevented and treated with vasoactive and inotropic medications.[4]

Vasoactive and inotropic medications are used in 90% of post-operative admissions to the paediatric cardiac ICU.[6,7] The most frequently used drugs include epinephrine, dopamine, dobutamine, milrinone, and vasopressin; a median of three vasoactives are typically used per patient and admission.[6,7] While studies have shown the value of certain inotropes in specific populations, no inotropes or vascoactive medications are labelled by the United States of America Food and Drug Administration or the European Medicines Agency for the prevention or treatment of low cardiac output syndrome in children.[8] Instead, the choice of which inotrope or vasoactive, as well as the dose, timing, and duration of administration of these medications are highly variable and mostly driven by the provider and institutional preference.[9] In addition, adjunct medications that modulate targets upstream or downstream of inotrope and vasoactive receptors are sometimes used to reduce vasoactive exposure despite limited evidence of efficacy (Table 1).[10] The purpose of this systematic review is to summarise the existing literature on clinical trials with endpoints related to post-operative administration of inotropes and vasoactives in children after cardiopulmonary bypass surgery to help inform both clinical practice and the design and conduct of future trials.

Table 1. Drugs included in this review and summary of their molecular mechanisms and net physiologic effects.

Drug class	Example	Mechanism and site of action	Effect
Adrenergic medications	Epinephrine	Stimulates α and β receptors in cardiomyocytes and vascular smooth muscle cells	Inotropy, chronotropy, and vasoconstriction
	Dopamine	Stimulates α and β receptors in cardiomyocytes and vascular smooth muscle cells	Inotropy, chronotropy, and vasoconstriction
	Dobutamine	Stimulates α and β receptors in cardiomyocytes	Inotropy and chronotropy
	Phenoxybenzamine	Binds to α receptors in vascular smooth muscle cells	Vasodilation
	Phentolamine	Competitively inhibits α receptors in vascular smooth muscle cells	Vasodilation
Vasopressin	Vasopressin	Binds to vasopressin receptors on vascular smooth muscle cells	Vasoconstriction
Calcium and calcium modulators	Calcium	Increases extracellular calcium	Inotropy and vasoconstriction
	Levosimendan	Binds to troponin C and increases sensitivity to calcium in cardiomyocytes	Inotropy and vasoconstriction
cAMP modulators	Milrinone	Inhibits phosphodiesterase 3 to increase cAMP on myocardium and vascular smooth muscle fibers	Inotropy and vasodilation (Inodilation)
cGMP modulators	Nesiritide	Inhibits RAS to stimulate cGMP in vascular smooth muscle cells	Vasodilation
	Nitroprusside	Formation of NO which increases cGMP in smooth muscle cells	Vasodilation

cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate

Materials and methods

Search strategy

PubMed and EMBASE were searched to identify studies that had the primary goal of investigating medications used for vasoactive support for paediatric patients after cardiac surgery with cardiopulmonary bypass. Studies from the years 2000 to 2020 were included. The patient population was defined as birth to 18 years of age, and identified using a controlled vocabulary and keywords related to "pediatrics." The patient population was further refined using keywords related to "postoperative care," "cardiac surgery," and "cardiopulmonary bypass." This population was then searched for vasoactive medications using the keywords "vasodilator OR vasorelaxant" and "cardiotonic agents OR inotrope OR cardiac stimulant." Animal studies; pre- or intra-operative medication administration; studies other than English; and case reports, letters, editorials, and comments were excluded. The search strategies are shown in the Appendix. The literature search included multiple classes of medications. Primary reviewers selected those pertaining to inotropic and vasoactive medications for screening for this paper. A total of 420 studies were identified.

Study selection

Identified articles were imported into EndNote. The title of each study was screened. Studies were included if they focused on vasoactive support for a medication administered in the post-operative period and excluded if they focused on a medication from a different class or if the medication was administered pre- or intra-operatively. Referenced articles were also screened and included if they met the search and selection criteria.

Two reviewers independently reviewed the abstracts of 51 studies to determine final eligibility. Papers were rejected if they did not report a primary endpoint related to vasoactive support for a medication administered in the post-operative period. A total of 37 papers were included in the final analysis (Fig 1).

Data extraction and study classification

A standardised data collection form was used to extract data from each eligible study. The following data were collected: study characteristics (including years of study and study design), study population characteristics (including age and cardiac defects), intervention (including medication administered), and study endpoints and results.

All studies included were primary research studies. Studies were further classified as prospective or retrospective, single or multicentre, randomised or non-randomised, placebo-controlled or not placebo-controlled, and blinded or non-blinded. For each medication, the dose, timing of administration, primary outcomes, and secondary outcomes were compiled and analysed.

Results

A total of 37 studies met our selection criteria: 20 studies were prospective, 17 were retrospective, 9 were placebo-controlled, 2 were multi-arm clinical trials, 32 (Table 2)[11–47] had a measure of efficacy as the primary outcome, including 2 studies that evaluated mortality as a primary outcome. Five studies focused on safety and side effects (Table 3).[11,19–21,25,38,47]

Collectively, selected studies reported on 12 medications in 2856 children: 15 studies focused on neonates or infants, and included 969 patients; 12 studies specified a surgical repair or congenital heart defect as part of the study population, including 5 studies that included only Norwood patients. All medications were given between the end of a bypass through the first 72 hours postoperatively. There was a wide variance in specific timing, dosing, and duration of treatment.

Adrenergic pathway targeting agents

Epinephrine, norepinephrine, and dopamine are alpha (α) and beta-(β) receptor agonists that promote inotropy and peripheral vasoconstriction in a dose-dependent manner.[6,48–52] These drugs

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Table 2. Selected inotropic and vasoactive drug trials in children after cardiac surgery.

Medication studied	Reference (Author; year)	Study design	N	Study population	Primary aim and intervention	Findings
Dopamine, Epinephrine, Milrinone, Vasopressin	McFerson et al; 2014[11]	• Single centre • Retrospective	65	Neonates (mean 5.5 days old) undergoing Norwood procedure from 2008 to 2012	Safety of dopamine, epinephrine, milrinone, and vasopressin administration, doses not specified	Tachyarrhythmias are associated with higher doses of milrinone and longer duration of epinephrine.
Epinephrine	Oualha et al; 2014[12]	• Single centre • Prospective	39	Children of 0–18 years old (mean 3.9 months) undergoing cardiac surgery with CPB who required epinephrine post-operatively 2011	Efficacy of epinephrine infusion of 0.01 µg/kg/minute to 0.23 µg/kg/minute (mean 0.07 µg/kg/minute) for 1–13 days (mean 1.5 days)	After epinephrine administration, HR increased from 135 to 159 and MAP increased from 51 to 66. Glucose and lactate levels increased significantly. All patients were also on milrinone. 9/39 developed LCOS.
Docarpamine	Watarida et al; 2000[13]	• Single centre • Prospective	11	Children undergoing cardiac surgery who were started on dopamine at 5 µg/kg/minute	Safety of docarpamine bolus 40 mg/kg every 8 hours while weaning off of dopamine infusion	No change in measured variables with docarpamine, which included MAP, right atrial pressure, mixed venous oxygen saturation, urine volume, and arrhythmias. Plasma concentrations were similar to dopamine infusion.
Dopamine	De Souza et al; 2001[14]	• Single centre • Prospective • Non-randomised	10	Children of 1.4 years–7.2 years old (mean 3.4 years) undergoing elective cardiac surgery with CPB	Efficacy of dobutamine high dose (10 mcg/kg/minute) versus low dose (5 mcg/kg/minute) versus placebo for 24 hours	Intramucosal pH values measured with gastric tonometer Intramucosal pH increased in the high dose group at 12 and 24 hours but was not statistically significant.
Dopamine, Milrinone	Cavigelli-Brunner et al; 2018[15]	• Single centre • Prospective • Randomised and double blinded	50	Children of 0.2–14.2 years old (median 1.2 years) undergoing open-heart surgery for congenital heart disease	Efficacy of dobutamine (infusion of 6 µg/kg/minute for 24 hours) versus milrinone (50 µg/kg followed by an infusion of 0.75 µg/kg/minute for 24 hours)	No difference in LCOS (as defined by the need for additional vasoactive support), length of mechanical ventilation, LOS, heart rate, or arrhythmias between the two groups. The dobutamine group had higher rates of nitroprusside usage.
Dobutamine, Levosimendan	Ebade et al; 2013[16]	• Single centre Prospective Randomised and open label	50	Children of 7 months–3.1 years old (mean 1.5 years) undergoing CPB for ASD or VSD repair with PAP > 50% SBP in 2011–2012	Efficacy of levosimendan (15 mcg/kg over 10 minutes followed by an infusion at 0.1–0.2 mcg/kg/minute) versus dobutamine (10 mcg/kg/minute)	Levosimendan was superior with increased CI and decreased PAP at 1 hour and 20 hours in the levosimendan group. No difference was noted in the duration of mechanical ventilation or LOS.
Phenoxy-benzamine (POB)	De Oliviera et al; 2004[17]	Single centre Retrospective Cohort study	105	Infants of 1 day-5.8 months old (median 7.5 days) undergoing the Norwood procedure from 1996 to 2002	Efficacy of POB (0.25 mg/kg followed by an infusion of 0.5–1 mg/kg/24 hours for 24 hours) in 42 patients compared to no POB in 63 patients	POB was associated with a decrease in sudden circulatory collapse (as defined by the need for ECMO and/or cardiac arrest) from 31% to 5% with a p-value of ≤0.002. POB patients were recruited from 1999 to 2002.
Phentolamine, Nitroprusside	Furck et al; 2010[18]	• Single study • Retrospective • Cohort study	146	Infants undergoing a Norwood procedure from 1996 to 2007	Efficacy of sodium nitroprusside for median 48 hours (4–173) with or without deep hypothermia versus phentolamine for median 72 hours (range 24–201) without deep hypothermia.	The phentolamine group had lower MAP and coronary perfusion pressure is compared to the deep hypothermia nitroprusside group. Similar rate of complications (hypoxic, haemodynamic, and/or neurological events). Phentolamine patients recruited from 2003 to 2007.

(*Continued*)

Table 2. (*Continued*)

Medication studied	Reference (Author; year)	Study design	N	Study population	Primary aim and intervention	Findings
Vasopressin	Lechner et al; 2007[19]	• Single centre • Retrospective	17	Term neonates of 3–12 days old (median 6 days) undergoing cardiac surgery for congenital heart disease with catecholamine-resistant shock from 2003 to 2005	Efficacy of vasopressin initiated at 0.05–0.2 mU/kg/minute (median 0.1 mU/kg/minute) and titrated up to 0.1–1.0 mU/kg/minute (median 0.3 mU/kg/minute) at median of 16 hours post-operatively	After initiation of vasopressin, MAP increased from a mean of 49 ± 8 to 69 ± 7. Inotrope requirement and volume requirement significantly decreased, and UOP significantly increased. No significant change in sodium was noted.
	Agrawal et al; 2012[20]	• Single centre • Prospective	12	Children of 1 month–8 years old (median 3 months) with signs of refractory vasodilatory shock after CPB	Efficacy of vasopressin infused at 0.5–3.0 mU/kg/minute for >60 minutes	After initiation of vasopressin, MAP increased from a mean of 41 ± 6 to 1) 57 ± 8 after 4 hours of treatment, 2) 62 ± 8 after 12 hours of treatment, and 3) 72 ± 9 after 24 hours of treatment. Decrease in inotropic support was noted at 1 hour and 24-hour time points. Sodium and UOP remained stable.
	Burton et al; 2011[21]	• Single centre • Retrospective	28	Neonates (mean 6 days old) undergoing Norwood procedure with worsening perfusion despite inotrope administration from 2007 to 2010	Efficacy of vasopressin infusion at 0.3 mU/kg/minute titrated to 0.1–1.2 mU/kg/minute (mean of 0.5 mU/kg/minute ± 0.3 mU/kg/minute)	After initiation of vasopressin, increased systolic BP (noted at 3 hours), increased urine output (noted at 2 hours), improved fluid balance (at 3 hours), decreased lactate, increased pH with all these changes sustained at 24 hours. No increase in heart rate or inotrope requirement.
	Alten et al; 2012[22]	• Single centre • Retrospective • Cohort study	37	Consecutive infants who underwent either Norwood or arterial switch procedure from 2008 to 2010	Efficacy of vasopressin infusion (0.3 mU/kg/minute started at 0 hours in 19 infants) post-operatively versus control group (18 infants)	The vasopressin group had higher cerebral oxygen levels (determined by near-infrared spectroscopy), lower lactates, lower inotropic support, and lower fluid resuscitation requirement in the first 24 hours, and shorter time to negative cumulative fluid balance.
	Lu et al; 2018[23]	• Single centre • Retrospective • Consecutive study	70	Children with vasodilatory shock after cardiac surgery from 2013 to 2015	Efficacy of vasopressin infusion at 0.2–2 mU/kg/minute	Initiation of vasopressin was associated with increased BP at 2 hours, and a trend towards increased PVR, decreased fluid requirement, increased urine output, and decreased lactate levels.
	Mastropietro et al; 2013[24]	• Single centre • Retrospective	34	Children of 0–6 years	Efficacy of vasopressin, dose not specified	MAP increased by 32 % with a decrease in mean vasoactive score. Efficacy was associated with administration of vasopressin at mean of 20 post-operative hours (non-responders had mean 6 hours).
	Davalos et al; 2013[25]	• Single centre • Retrospective • Cohort study	78	Children of 0–6 years (mean of 5.2 months for the study group and 6.1 months for the control group) undergoing surgery for complex CHD from 2009 to 2010	Safety of vasopressin infusion (0.3–2 mU/kg/minute) for 41 ± 24 hours post-operatively versus control group with the same Aristotle basic complexity score and LOS	Serum sodium decreased more quickly and to a greater extent in patients who received AVP (mean sodium of 134 compared to 137). Forty-eight percent of the patients treated with AVP were hyponatremic compared to 17% in the control group.

Calcium	Murray et al; 2019[26]	• Single centre • Retrospective • Cohort study	82	Infants of 0–30 days old undergoing cardiac surgery and not on ECMO from 2016 to 2018	Efficacy of calcium infusion, variable dose, not specified, versus control group	Vasoactive infusion score was measured for the first 24 hours post-operatively. Post-operative cardiac arrest rate of 0% in the calcium group and 12.2% in the control group ($p = 0.03$). No difference in hospital LOS, duration of mechanical ventilation, or operative mortality.
Levosimendan	Ricci et al; 2012[27]	• Single centre • Prospective • Randomised, open-label	63	Neonates (mean 17 days) with RACHS 3 or 4 procedures from 2008 to 2010	Efficacy of levosimendan infusion of 0.1 μg/kg/minute for 72 hours versus control group	The levosimendan group had lower lactate levels and lower inotrope scores compared to the control. LCOS was reported to be 37% in the levosimendan group and 61% in the control group.
	Amiet et al; 2018[28]	• Single centre • Retrospective	62	Children of 1 day–14 years (median 0.5 years) undergoing CPB with the administration of levosimendan from 2005 to 2013	Efficacy of levosimendan infusion at 0.1 μg/kg/minute without a bolus for 48 hours. If tolerated, dose was increased to 0.2 μg/kg/minute for 24 hours.	At 24 hours after levosimendan infusion, diuresis and SvO2 improved significantly, and lactate was found to be significantly decreased.
	Tkachuk et al; 2011[29]	• Single centre • Retrospective • Cohort study	170	Neonates undergoing TAPVR complete repair or arterial switch operation from 2003 to 2011	Efficacy of levosimendan 0.1 μg/kg/minute in 32 patient versus control group	No difference in left ventricular ejection fraction. The levosimendan group had lower inotropic support duration, mechanical ventilation duration, and ICU stay. No difference in mortality.
	Giordano et al; 2013[30]	• Single centre • Retrospective • Case–control study	92	Children undergoing elective cardiac surgery with CPB from 2010 to 2012	Efficacy of levosimendan infusion 0.1 μg/kg/minute versus 72 hours compared to control group	The levosimendan group had a statistically significant lower heart rate, higher mixed venous oxygen saturation, lower lactate, lower inotropic score, shorter intubation time, and shorter LOS.
	Osthaus et al; 2009[31]	• Single study • Retrospective	7	Infants of 7 days–211 days (mean 29 days) undergoing cardiac surgery with severe myocardial dysfunction	Efficacy of levosimendan 12 mcg/kg loading dose followed by infusion of 0.2 mcg/kg/minute over 24 hours as rescue therapy	Levosimendan administration did not affect heart rate, MAP, or CVP. Mean lactate decreased and central venous oxygenation increased at 24 and 48 hours from baseline.
	Wang et al; 2019[32]	• Single centre • Prospective • Randomised, double blinded, placebo controlled	187	Children of 0–48 months undergoing cardiac surgery from 2018 to 2019	Efficacy of levosimendan infusion (0.05 μg/kg/minute) for 48 hours versus placebo	The levosimendan group showed no increase in adverse outcomes (hypotension, arrhythmias, hypotension) and no benefit in the duration of mechanical ventilation, LCOS, or 90-day mortality.
Levosimendan, Milrinone	Momeni et al; 2011[33]	• Single centre • Prospective • Randomised, double blinded	36	Children of 0–5 years (median 4 months) undergoing CPB for CHD and requiring inotropes from 2008 to 2009	Efficacy of levosimendan infusion (0.05 μg/kg/minute) compared to milrinone infusion (0.4 μg/kg/minute) for up to 48 hours post-operatively	The levosimendan group had a lower mean heart rate and no difference in lactate levels.
	Basto-Duarte et al; 2017[34]	• Single centre • Restrospective	55	Neonates of 0–38 days (mean 5 days in the study group and 1.5 days in the control group); Norwood procedures from 2009 to 2015	Efficacy of levosimendan (17 patients) versus milrinone (38 patients)	Levosimendan had in-hospital mortality of 17.7% compared to 50% (p-value 0.036) and decrease in renal failure 23.5% compared to 54.1% (p-value 0.036). No difference in 30-day mortality.
	Pellicer et al; 2013[35]	• Single centre • Prospective • Randomised, double blinded	20	Neonates of 6–34 days undergoing CPB with stable pre-operative haemodynamics from 2009 to 2010	Efficacy of levosimendan (0.1 mcg/kg/minute increased to 0.2 mcg/kg/minute at 2 hours) versus milrinone (0.5 μg/kg/minute increased to 1.0 μg/kg/minute at 2 hours)	The levosimendan group had lower heart rates with no difference in rate pressure index (heart rate × MAP). Milrinone group had significantly higher lactate and lower pH at 6 hours, and higher inotrope requirement at 6 and 12 hours.
	Jadhav et al; 2012[36]	• Single centre • Retrospective • Cohort study	14	Children of 0 years–18 years undergoing cardiac surgery	Efficacy of levosimendan versus milrinone doses is not specified	The levosimendan group required more inotropic support and had a longer ICU stay.

(*Continued*)

Table 2. (*Continued*)

Medication studied	Reference (Author; year)	Study design	N	Study population	Primary aim and intervention	Findings
	Lechner et al; 2012[37]	• Single-centre • Prospective • Randomised, double blinded	40	Infants of 0–12 months (mean 10 weeks) undergoing cardiac surgery with CPB 2012	Efficacy of levosimendan infusion (0.1 mcg/kg/minute) compared to milrinone infusion (0.5mcg/kg/minute) for 24 hours	No difference between groups in cardiac index during the first 48 hours. No difference in inotrope requirement or urine output. No patients developed LCOS in either group
	Thorlacius et al; 2019[38]	• Two-centre • Prospective • Randomised, double blinded	71	Infants of 1–12 months (mean 5.8 months) undergoing Tetrology of Fallot, complete AVSD, or VSD repair with CPB 2014–2017	Efficacy of levosimendan (12 μg/kg bolus followed by 0.1 μg/kg/minute infusion) versus milrinone (48 μg/kg bolus followed by 0.4 μg/kg/minute infusion)	No significant difference in inotropic requirements, lactate, rates of acute kidney injury, or fluid overload.
Milrinone	Duggal et al; 2005[39]	• Single centre • Prospective • Non-randomised, and open label, consecutive	15	Children of 0.2–16 months (median 7 months) with LCOS after cardiac surgery from 2001 to 2003	Efficacy of milrinone infusion at 0.3 – 0.6 μg/kg/minute started 3 hours postop if LCOS identified	Biventricular systolic function (defined by myocardial performance index and measured by Doppler ECHO) significantly increased at 18–24-hour post-operatively with no effect on mean heart rate or mean ventricular ejection fraction
	Hoffman et al; 2003[40]	• Multicentre (31 centres) • Prospective • Randomised, double blinded, placebo-controlled multiple arm	238	Children of 2 days–6.9 years (median 3 months) undergoing biventricular repair of cardiac lesions with CPB	Efficacy of low dose milrinone (25 μg/kg bolus followed by 0.25 μg/kg/minute), versus high dose milrinone (75 μg/kg bolus followed by 0.75 μg/kg/minute) versus placebo within 90 minutes of post-operative admission	The high dose milrinone significantly reduced the risk of LCOS (tachycardia, oliguria, poor perfusion, or cardiac arrest) within 36-hour post-op compared to placebo. No difference in time of intubation, but fewer milrinone patients had a prolonged hospital course. No increase in arrhythmias.
	Garcia Guerra et al; 2013[41]	• Single centre • Prospective • Cohort study	63	Infants with IQR 0 months–6 months (median 3 months) undergoing CPB and on milrinone infusion	Safety of milrinone infusion 0.5–0.75 μg/kg/minute with or without an intra-operative loading dose of 0.25–0.5 μg/kg. Serum milrinone levels were measured at 9–12 hours, 18–24 hours, 40–48 hours, and infusion ends.	Sixteen percent of the patients had suprathera-peutic milrinone levels at 40–48 hours of treatment with milrinone, and these patients were more likely to have LCOS (lactate greater than 2 mmol/L or arterio-venous oxygen difference of greater than 30%). An additional 36% of patients had a subtherapeutic milrinone level.
	Barnwal et al; 2017[42]	• Single centre • Prospective • Randomised, double blinded	90	Children of 6 weeks–1.9 years undergoing cardiac surgery and with PAP > 50 mmHg on Doppler ECHO	Efficacy of fixed bolus dose milrinone (50 mcg/kg) during rewarming. After CPB, patients were randomised to low dose (0.375 μg/kg/minute), medium dose (0.5 μg/kg/minute), or high dose (0.75 μg/kg/minute) for 24 hours	The high dose group needed higher inotrope support compared to the other groups, with no difference in length of ICU stay or duration of ventilatory support, mean airway pressure, and OI showed no difference between groups at 24 hours. The high dose group required higher doses of inotropes.
	Chu et al 2000[43]	• Single centre • Prospective study	10	Children undergoing Tetrology of Fallot repair with post-bypass PAP > 50% of systolic arterial pressure	Efficacy of milrinone 20 μg/kg loading dose followed by 0.2 μg/kg/minute infusion versus control group	Milrinone group had a significant reduction in the PAP/SBP ratio within 15 minutes, which persisted for 24 hours during the continuous infusion of milrinone.
	Smith et al; 2011[44]	• Single centre • Prospective	603	Consecutive patients of 0 years–35 years (median 5.5 months) with CHD surgery from 2007 to 2010	Safety of milrinone (usually with 50 μg/kg bolus) at a continuous rate between 0.25 and 1.0 μg/kg/minute	Odds ratio for tachyarrhythmia after treatment with milrinone was 2.8, independent of age, duration of cross-clamp time, or the use of epinephrine or dopamine.

Nesiritide, Milrinone	Costello et al; 2014[45]	• Single centre • Prospective • Randomised, double-blinded, placebo-controlled, multi-arm, parallel group controlled	106	Children of 1.8 years–15.2 years (median 2.7 years) undergoing Fontan operations	Efficacy of nesiritide (2 μg/kg followed by 0.015 μg/kg/minute infusion up to 0.03 μg/kg/minute) versus milrinone (50 μg/kg loading dose followed by 0.5 μg/kg/minute infusion) or placebo	No improvement in outcomes as defined by mean days alive and out of the hospital in either treatment group. There were no differences in any of the secondary outcomes (cardiac index, lactate, inotrope score, or urine output).
Nesiritide	Simsic et al; 2006[46]	• Single centre • Prospective	17	Children of 0.3 years–14 years (mean 8 years) undergoing tetralogy of Fallot, VSD, or mitral valve repair with CPB	Efficacy of nesiritide 0.1 μg/kg loading dose followed by infusion of 0.01 μg/kg/minute for 6 hours then 0.02 μg/kg/minute for 18 hours	MAP decreased by 7% after nesiritide.
Nitroprusside	Moffett et al; 2008[47]	• Single centre • Retrospective	63	Children of 0–18 years undergoing cardiac surgery and administration of nitroprusside	Safety of nitroprusside administration, dose not specified	Cyanide levels are measured in the serum. Toxic cyanide levels found in 11% of patients (7/63). Mean dose of nitroprusside is the best predictor of elevated cyanide levels.

ASD = aortic septal defect; AVP = arginine vasopressin; BP = blood pressure; CHD = congenital heart disease; CI = confidence interval; CPB = cardiopulmonary bypass; ECHO = echocardiogram; ECMO = extracorporeal membrane oxygenation; HR = heart rate; ICU = intensive care unit; IQR = interquartile range; LCOS = low cardiac output syndrome; LOS = ; MAP = mean arterial pressure; OI = ; PAP = pulmonary artery pressure; POB = phenoxybenzamine; PVR = pulmonary venous return; RACHS = risk adjustment in congenital heart surgery score; SBP = systolic blood pressure; SvO2 = mixed venous oxygen saturation; TAPVR = total anomalous pulmonary venous return; UOP = urine output; VSD = ventricular septal defect

Table 3. Adverse events were reported in the reviewed studies.

Medication studied	Reference (author; year)	Study design	n	Study population	Adverse event of interest	Findings
Epinephrine, Dopamine, Vasopressin, Milrinone	McFerson et al; 2014[11]	• Single centre • Retrospective	65	Neonates (mean 5.5 days old) undergoing Norwood procedure from 2008 to 2012	Arrhythmia	Associated with longer duration of infusion of epinephrine and higher doses of milrinone (>0.75 μg/kg/minute), no association with dopamine or vasopressin
Vasopressin	Lechner et al; 2007[19]	• Single centre • Retrospective • Observationalobservational	17	Term neonates of 3–12 days old (median 6 days) undergoing cardiac surgery for congenital heart disease with catecholamine-resistant shock from 2003 to 2005	Hyponatremia, Acute kidney injury	Not associated; vasopressin initiated at 0.05–0.2 mU/kg/minute (median 0.1 mU/kg/minute) and titrated up to 0.1–1.0 mU/kg/minute (median 0.3 mU/kg/minute) at median of 16 hours post-operatively
	Agrawal et al; 2012[20]	• Single centre • Prospective • Observational	12	Children of 1 month–8 years old (median 3 months) with signs of refractory vasodilatory shock after CPB	Hyponatremia, Acute kidney injury, Transaminitis, Coagulopathy, Thrombocytopenia	Associated with transient thrombocytopenia that was not clinically significant. Not associated with other markers; vasopressin infused at 0.5–3.0 mU/kg/minute for >60 minutes.
	Burton et al; 2011[21]	• Single centre • Retrospective • Observational	28	Neonates (mean 6 days old) undergoing Norwood procedure with worsening perfusion despite inotrope administration from 2007 to 2010	Hyponatremia, Transaminitis	Associated (mean 144 to 135), not clinically significant; vasopressin infusion at 0.3 mU/kg/minute titrated to 0.1–1.2 mU/kg/minute (mean of 0.5 mU/kg/minute ± 0.3 mU/kg/minute)
	Davalos et al; 2013[25]	• Single centrer • Retrospective • Cohort study	78	Children of 0–6 years (mean of 5.2 months for the study group and 6.1 months for the control group) undergoing surgery for complex CHD 2009–2010	Hyponatremia	Associated (mean 137 to 134), not clinically significant; vasopressin infusion (0.3–2 mU/kg/minute) for 41 ± 24 hours post-operatively
Levosimendan, Milrinone	Thorlacius et al; 2019[38]	• Two-centre • Prospective • Randomised, double blinded	71	Infants of 1–12 months (mean 5.8 months) undergoing Tetrology of Fallot, complete AVSD, or VSD repair with CPB 2014–2017	Acute kidney injury	Unclear association; levosimendan (12 μg/kg bolus followed by 0.1 μg/kg/minute infusion) versus milrinone (48 μg/kg bolus followed by 0.4 μg/kg/minute infusion)
Nitroprusside	Moffett et al; 2008[47]	• Single centre • Retrospective	63	Children of 0–18 years undergoing cardiac surgery and administration of nitroprusside	Cyanide levels	Associated; dose not specified.

AVSD = atrioventricular septal defect; CHD = congenital heart disease; CPB = cardiopulmonary bypass; VSD = ventricular septal defect

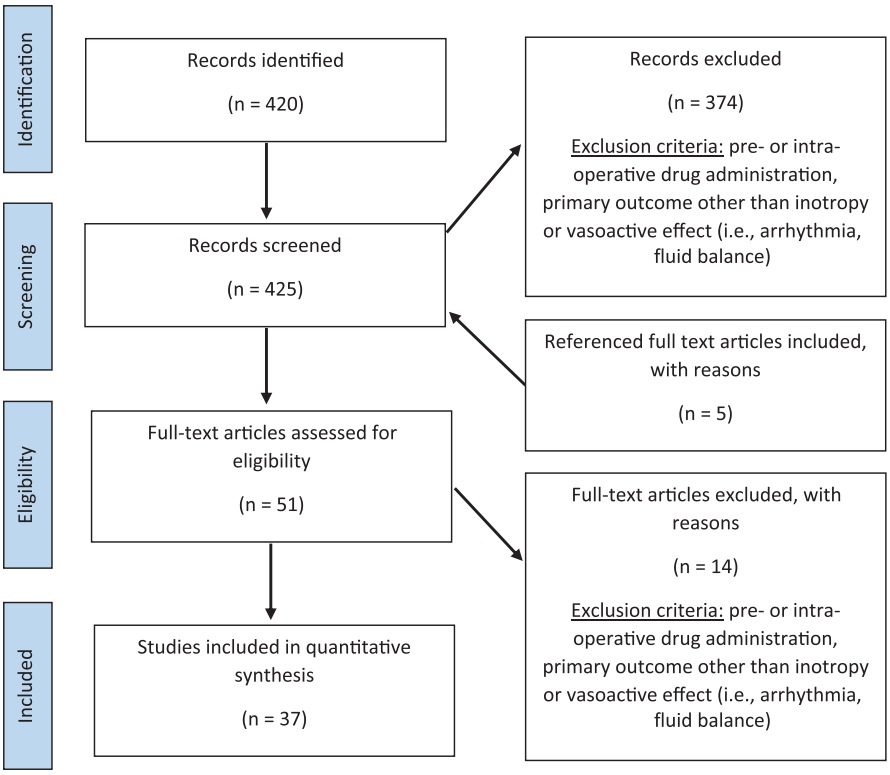

Figure 1. Summary of literature search strategy and results.
Search parameters: all trials from 2000 to 2020 are in English with a medication (inotrope, vasoactive) and cardiac surgery and post-operative care and paediatrics.

are commonly used in the post-operative cardiac care of children,[6,7] but only 1 study to date investigated the efficacy of epinephrine[12] and no studies were found on the efficacy of norepinephrine or dopamine. In a study of 39 children, epinephrine dosages of 0.01–0.23 μg/kg/minute was not shown to prevent post-operative low cardiac output syndrome.[12] Docarpamine, an oral dopamine precursor which degrades to stable dopamine levels in the serum,[13] was found to be safe in 11 post-operative children, but there was no control arm to evaluate efficacy and the drug is only available in Japan.[13]

Dobutamine is a synthetic β agonist, which promotes inotropy and chronotropy.[10,51,53,54] A total of 3 prospectives, including 2 with randomisation between arms, clinical trials of dobutamine enrolled a combined total of 110 children 0–18 years of age.[14–16] None of these studies demonstrated a clinical benefit of dobutamine using dosages of 6–10 μg/kg/minute. Dobutamine was not superior to milrinone in preventing low cardiac output syndrome in 50 children undergoing elective cardiac repair,[15] and was inferior to levosimendan in increasing cardiac index in 50 children with elevated pulmonary arterial pressures undergoing atrial septal defect or ventricular septal defect repair.[16] Furthermore, dobutamine showed no significant increase in splanchnic perfusion as measured by gastric tonometry in 10 post-operative children.[14]

Phenoxybenzamine and phentolamine, irreversible and reversible α blockers, respectively, were used for afterload reduction after the Norwood operation.[55–58] In a single trial of 105 infants undergoing stage 1 surgical palliation for single-ventricle CHD, patients were consecutively recruited to receive phenoxybenzamine or not. There was a decrease in the sudden circulatory collapse in the group of infants who received phenoxybenzamine compared to the negative control.[17] Phentolamine was studied against nitroprusside in 146 post-operative Norwood infants and showed lower mean arterial blood pressure and coronary perfusion pressure; however, deep hypothermia was used in the nitroprusside group only and may have confounded the results.[18]

One study looked at the association of tachyarrhythmias and adrenergic agent use in 65 Norwood patients. The prolonged use of epinephrine in the post-operative period was associated with an increased risk of tachyarrhythmias.[11] Dopamine, norepinephrine, and vasopressin were included as covariates in the study analysis, but the overall association was only reported for epinephrine.

Vasopressin

Vasopressin activates V1 receptors in vascular smooth muscle to activate protein kinase C, increasing intracellular calcium, and producing smooth muscle contraction.[59,60] Vasopressin may have fewer proarrhythmic effects compared to catecholamines and may be more efficacious in catecholamine-refractory shock.[61] Seven studies of vasopressin met our inclusion criteria, of which 1 was a prospective trial. The dosing of vasopressin ranged from 0.05 to 3 mU/kg/minute. Vasopressin reproducibly increased blood pressure in 127 post-operative cardiac infants and children with refractory shock.[19–21,23] In four out of the five studies, other inotropes were able to be weaned without any adverse effects.[19–21,23,24] Administration of vasopressin was also correlated with signs of improved systemic perfusion including decreased lactate, increased pH, and decreased fluid requirement.[21,23] In a retrospective study of 37 consecutive infants undergoing the Norwood or arterial switch operation,

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vasopressin was started de facto rather than as rescue therapy, and was likewise associated with improvements in systemic perfusion including lower lactates, higher cerebral oxygen levels, and decreased fluid requirements compared to historical controls.[22] No study reported clinically significant hyponatremia with the administration of vasopressin.[19–21,25]

Calcium, calcium sensitisers, and cAMP pathway targeting agents

A total of 22 studies investigated calcium or modulators of the calcium cyclic adenosine monophosphate pathway. Calcium infusion, directly and indirectly, increases blood pressure, by way of increasing serum calcium and by cyclic adenosine monophosphate excretion.[26,62,63] A retrospective cohort study on calcium administration in 82 infants found that the administration of parenteral calcium was associated with a decrease in post-operative cardiac arrest compared with historical controls.[26] The mean ionised calcium level was 1.33 mmol/L in the study group compared to 1.24 mmol/L in the control group.

Levosimendan is a calcium sensitiser, binding to the cardiac troponin C protein and preventing binding of troponin I for sustained cardiac myocyte contraction.[64–66] We examined 13 studies on 867 patients focused on the administration of levosimendan[10,16,28–30,32–34,36–38]: 7 studies were retrospective, and 6 were prospective randomised controlled trials. The dosing range was 0.05–0.2 μg/kg/minute for 48–72 hours with or without a loading dose of 12–15 μg/kg. The median dose was 0.1 μg/kg/minute. There was mixed data on the effects of levosimendan on heart rate, mean arterial blood pressure, cerebral oxygenation, and lactate level. Overall, three studies showed that levosimendan may be effective at preventing low cardiac output syndrome when used as an adjunct therapy to other vasopressors.[27,28,30]

Milrinone inhibits phosphodiesterase type III which increases levels of cyclic adenosine monophosphate and calcium uptake into cells, leading to inotropy and peripheral vasodilation.[67–70] Milrinone has been studied in 12 prospective and 3 retrospective studies, both as a primary agent and as rescue therapy in children after cardiopulmonary bypass, totaling 1476 patients. Dosing was variable, with a range of 0.25–1.0 μg/kg/minute with or without a loading dose of 20–50 μg/kg. Two studies suggested that milrinone may prevent low cardiac output syndrome[39,40]; however, another study measured milrinone levels and found that 16% of treated patients had supratherapeutic levels, which was associated with higher rates of low cardiac output syndrome.[41] Milrinone has also been studied in children with pulmonary hypertension, and was found to decrease pulmonary arterial pressure in 2 studies.[42,43]

Nine trials on milrinone and levosimendan reported rates of low cardiac output syndrome as an endpoint. In a randomised, double-blind, placebo-controlled trial of 238 post-operative children, milrinone was shown to significantly decrease the risk of low cardiac output syndrome.[40] Milrinone also significantly increased biventricular function in 15 post-operative children who were at risk or developed low cardiac output syndrome.[39] Levosimendan showed no decrease in low cardiac output syndrome or mortality in a randomised, double-blind, placebo-controlled trial of 187 post-operative children.[32] However, 6 studies compared levosimendan to milrinone and showed mixed data regarding superiority.[33–38] Three studies were randomised controlled trials and 3 were retrospective for a total of 236 patients. There were no consistent differences in inotropic requirements or rates of low cardiac output syndrome between the levosimendan group and milrinone groups, and there was mixed data comparing rates of renal failure with levosimendan versus milrinone.[19,34,37,38] Nevertheless, five out of the six studies suggested that levosimendan is as safe and effective as milrinone. These studies had wide age variance, as well as variation in cardiac defects.

There is mixed evidence as to whether milrinone is associated with arrhythmias. A double-blind placebo-controlled study of 238 children found no association with arrhythmias, even with a loading dose followed by a high continuous infusion of milrinone at 0.75 μg/kg/minute.[40] Yet, a larger observational study of 603 paediatric patients after cardiac surgery found that milrinone administration is an independent risk factor for arrhythmias.[44]

Nitric oxide and cyclic guanosine monophosphate pathway targeting agents

Modulators of the cyclic guanosine monophosphate pathway have been studied both independently and in comparison to cyclic adenosine monophosphate modulators. Nesiritide is a synthetic brain natriuretic peptide that inhibits the renin–angiotensin aldosterone system and stimulates cyclic guanosine monophosphate, causing vasorelaxation.[71,72] There were 2 studies of nesiritide in 106 children. Dosing was variable, with a loading dose followed by infusion up to 0.03 μg/kg/minute. A loading dose of nesiritide decreased mean arterial pressure by 7% in a study of 17 children after cardiac surgery,[46] and was found to be equivocal when compared to milrinone in preventing low cardiac output syndrome in 106 children.[45] Nitroprusside releases nitric oxide, which increases the formation of cyclic guanosine monophosphate, causing vasorelaxation.[73–75] There were two retrospective studies on nitroprusside. Dosing was not prescribed but the mean starting dose was between 1 and 2 μg/kg/minute in these studies. One study found no increase in outcomes of complications compared to phentolamine.[18] In terms of safety, one study found that 11% of patients treated with nitroprusside were found to have toxic levels of cyanide.[47]

Discussion

Current knowledge gaps

We compiled data on 37 drug trials in 2856 children across 12 vasoactives and inotropes from 2000 to 2020. Our review found that overall evidence supporting the use of these drugs in children in the post-operative setting, including for the prevention or treatment of low cardiac output syndrome, is limited. The majority of studies were small sample size and underpowered for effect size, less than half were randomised, and safety and efficacy endpoints differed widely, limiting the ability to combine data for meta-analyses.

Only 2856 children were enrolled across all studies, and only 2 studies were multicentre trials. These findings are despite the fact that according to the Society of Thoracic Surgeons database, >22,000 children undergo cardiopulmonary bypass surgery each year, and that by previously published estimates, 90% of post-operative paediatric patients receive inotropes or vasoactives.[6,76] While reasons for the relative lack of studies are likely multifactorial, low consent rates, cost, and current study designs that interfere with the complex and high stakes clinical care delivered in the post-operative setting are likely key drivers.[8,77] Parental, as well as provider, stress, and anxiety, coupled with children being at significant medical and surgical risk while undergoing invasive procedures, is also likely to reduce consent rates.[78,79] Even for those patients who do get enrolled in a trial, study designs with extensive

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protocol-specific procedures may result in a large number of protocol deviations, study drop-outs, and decreased participation.[8]

When studies are conducted, elements of their design and endpoint selection may contribute to the inability to identify significant efficacy or safety signals. Only 11 of the included studies were designed with a randomised controlled arm, limiting their ability to draw definitive conclusions about efficacy.[80] Two studies employed serial recruitment of each cohort, such as the studies investigating the use of afterload reduction in post-operative infants after the Norwood procedure, with time as an inherent confounder in these studies.[17,18,81] Furthermore, in an attempt to overcome limited enrollment, studies often included different cardiac lesions with variable physiologic states, as was the case for 25/37 studies included in our review. While information from combined populations may be helpful to guide overall practice, significant physiologic differences (e.g., between infants with systemic right versus left ventricles) may induce biases that, if left unadjusted, obscure drug efficacy or safety signals.[82,83]

The selection of consistent, meaningful endpoints remains elusive. Heart rate and blood pressure changes were used as primary endpoints in 12 of the 37 studies. While improvements in these biomarkers are likely of clinical significance, their relatively downstream position in the cardiovascular function cascade may obscure the important effects of studied drugs. Ultimately, clinical endpoints are needed to confirm the efficacy of interventions, but often require very large sample sizes to identify treatment effects in complex populations.[84] Under these circumstances, pooling data across studies and conducting meta-analyses may provide additional evidence. Low cardiac output syndrome is an endpoint strongly correlated with clinical outcomes, and was used as a primary or secondary endpoint in 16 of the 37 studies. Unfortunately, these studies used 7 different surrogate markers of low cardiac output, again making it difficult to compare results across studies.[4]

Future directions

Vasoactive and inotropic support are essential components of post-operative care for paediatric patients after cardiopulmonary bypass surgery. Underpowered studies have led to a history of negative trials,[8,77] and there is a paucity of data for the selection and dosing of vasoactives and inotropes for these patients. As a result, institutional preference rather than evidence-based medicine underlies many of the treatment decisions.[8,77] Innovations in clinical trials and paediatric drug development programs in other therapeutic areas may hint at solutions to address this knowledge gap.

First, pragmatic trial designs may limit interference with clinical care.[84,85] The post-operative period is typically a highly monitored environment, in which large amounts of clinical data are collected per routine medical care.[86] This creates an opportunity for leveraging standard of care physiologic monitoring, laboratory results, and cardiac function assessments (e.g., echocardiograms) in study designs. Wide assessment time windows rather than fixed time points, use of local clinical laboratories for biospecimen quantification, and data collection mechanisms that allow for uploading of care notes, imaging studies and interpretations, and other clinical data may all facilitate leveraging clinical data and minimise the need for study-specific procedures.[87] To alleviate concerns about site-based differences in assessments and result interpretations, a review of diagnostic studies and adjudication of events based on clinical documentation can be performed centrally under strict protocol guidance.[8,88] Ultimately, harnessing the vast amounts of data captured in the electronic health record will create opportunities for study designs with drastically reduced and simplified data acquisition and collection mechanisms. With large national efforts underway, clinical trials in children after cardiopulmonary bypass surgery may be an ideal target for such innovative approaches. Similar efforts leveraging data collected from a nationwide clinical registry (as opposed to an electronic health record), sometimes referred to as "trials within the registry," are currently being conducted in children after cardiac surgery.[89]

In addition to pragmatic trials, strategically designed registries may help support drug development. Again, leveraging existing data collection, or linking electronic health records across institutions into registries, as is done with the National Patient-Centered Clinical Research Network and similar initiatives, may limit the burden of such efforts.[90–95] A comprehensive database of clinical data, drug utilisation, and outcomes would help identify potential signals of efficacy and safety, aid in the design of clinical trials, and, for pragmatically designed trials, could serve as a data collection platform. Efforts to ensure rigorous and high-quality data collection, including adherence to regulatory guidance, where applicable, are essential to maximise the benefit of registries to drug development.[96] Importantly, the paediatric heart disease community has extensive experience and a track record of success leveraging registries, from the Society of Thoracic Surgeons Congenital Databases to wide-ranging efforts capturing all phases of cardiac care, through most recent efforts to organise and align registries as done through Cardiac Networks United.[97,98]

Finally, careful attention to individual clinical trial considerations, including simplified informed consent and electronic consent forms, incorporation of screening efforts to facilitate early consenting, and extensive education and training of site staff may improve enrollment rates and facilitate trial execution.[8,78] Standardised endpoints and definitions, such as for low cardiac output syndrome, will improve the ability for meta-analysis. Most significantly, efforts to engage patients and their families in the design and conduct of clinical trials can significantly impact both study quality and participation.[78]

In conclusion, knowledge gaps remain in the use of vasoactives and inotropes in post-operative paediatric cardiac care, but numerous recent innovations create opportunities to rethink the conduct of clinical trials in this high-risk population.

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Appendix

Search strategy:

Databases: EMBASE, EndNote

((((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR "evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tiab] OR evaluation studies[tiab] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case-control studies"[MeSH Terms] OR "case-control"[tiab] OR "cohort studies"[MeSH Terms] OR cohort[tiab] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tiab] OR "follow up"[tiab] OR "comparative study"[Publication Type] OR "comparative study"[tiab] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[mh] NOT humans[mh])) AND ("2000/01/01"[PDat] : "3000/12/31"[PDat]) AND English[lang])) AND ((((((drug therapy[sh] OR diuretics[mesh] OR diuretics [Pharmacological Action] OR diuretic[tiab] OR diuretics[tiab] OR anticoagulants[mesh] OR Anticoagulants [Pharmacological Action] OR anticoagul*[tiab] OR "thrombin inhibitors"[tiab] OR "thrombin inhibitor"[tiab] OR "Immunosuppressive Agents"[mesh] OR immunosuppression[mesh] OR "Immunosuppressive Agents"[Pharmacological Action] OR immunosuppressive OR immunosuppressants[tiab] OR immunosuppressant[tiab] OR immunosuppression[tiab] OR immunosuppressions[tiab] OR steroids[mesh] OR steroid*[tiab] OR analgesics[mesh] OR analgesics[Pharmacological Action] OR analgesic[tiab] OR analgesics[tiab] OR anesthetics[mesh] OR "Anesthetics"[Pharmacological Action] OR anesthetic[tiab] OR anesthetics[tiab] OR "Vasodilator Agents"[Mesh] OR "Vasodilator Agents"[Pharmacological Action] OR vasodilator[tiab] OR vasodilators[tiab] OR vasorelaxants[tiab] OR vasorelaxant[tiab] OR "vasoactive antagonists"[tiab] OR "vasoactive antagonist"[tiab] OR "Cardiotonic Agents"[Mesh] OR "Cardiotonic Agents" [Pharmacological Action] OR cardiotonic[tiab] OR inotrope*[tiab] OR "cardiac stimulants"[tiab] OR "cardiac stimulant"[tiab] Or cardiotonic*[tiab] OR "myocardial stimulant*"[tiab] OR "cardioprotective agent*"[tiab] OR "Hypoglycemic Agents"[mesh] OR "Hypoglycemic Agents"[Pharmacological Action] OR "hypoglycemic agent*"[tiab] OR antihyperglycemic*[tiab] OR "hypoglycemic drug*"[tiab] OR antidiabetic*[tiab])) AND (("Cardiopulmonary Bypass"[Mesh]) OR ("Cardiac Surgical Procedures"[Mesh] OR "cardiac surgery"[tiab] OR "heart surgery"[tiab] OR "cardiopulmonary bypass"[tiab]))) AND ("postoperative period"[mesh] OR "Postoperative Care"[mesh] OR "postoperative complications"[mesh] OR postoperative[tiab])) AND (("Pediatrics"[Mesh] OR pediatric[tiab] OR pediatrics[tiab] OR paediatric[tiab] OR paediatrics[tiab] OR juvenile[tiab] OR juveniles[tiab] OR "Infant"[Mesh] OR infant[tiab] OR infants[tiab] OR infantile[tiab] OR "Child"[Mesh] OR child[tiab] OR children[tiab] OR childhood[tiab] OR preadolescent[tiab] OR preadolescents[tiab] OR prepubescent[tiab] OR "Adolescent"[Mesh] OR adolescent[tiab] OR adolescents[tiab] OR youth[tiab] OR youths[tiab] OR teenager[tiab] OR teenagers[tiab] OR teenaged[tiab] OR teen[tiab] OR teens[tiab]) NOT ("Adult"[Mesh] NOT ("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh])))) AND ("2000/01/01"[PDat] : "3000/12/31"[PDat]) AND English[lang])

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Search strategy:

Databases: PubMed (MEDLINE)

Set #		Results
1	("Pediatrics"[Mesh] OR pediatric[tiab] OR pediatrics[tiab] OR paediatric[tiab] OR paediatrics[tiab] OR juvenile[tiab] OR juveniles[tiab] OR "Infant"[Mesh] OR infant[tiab] OR infants[tiab] OR infantile[tiab] OR "Child"[Mesh] OR child[tiab] OR children[tiab] OR childhood[tiab] OR preadolescent[tiab] OR preadolescents[tiab] OR prepubescent[tiab] OR "Adolescent"[Mesh] OR adolescent[tiab] OR adolescents[tiab] OR youth[tiab] OR youths[tiab] OR teenager[tiab] OR teenagers[tiab] OR teenaged[tiab] OR teen[tiab] OR teens[tiab]) NOT ("Adult"[Mesh] NOT ("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh]))	3581652
2	"postoperative period"[mesh] OR "Postoperative Care"[mesh] OR "postoperative complications"[mesh] OR postoperative[tiab] Test Perioperative? Intensive Care Units, Paediatric	794279
3	"Cardiac Surgical Procedures"[Mesh] OR "Cardiopulmonary Bypass"[Mesh] OR "cardiac surgery"[tiab] OR "heart surgery"[tiab] OR "cardiopulmonary bypass"[tiab]	228588
4	drug therapy[sh] OR diuretics[mesh] OR diuretics [Pharmacological Action] OR diuretic[tiab] OR diuretics[tiab] OR anticoagulants[mesh] OR Anticoagulants [Pharmacological Action] OR anticoagul*[tiab] OR "thrombin inhibitors"[tiab] OR "thrombin inhibitor"[tiab] OR "Immunosuppressive Agents"[mesh] OR immunosuppression[mesh] OR " Immunosuppressive Agents"[Pharmacological Action] OR immunosuppressive OR immunosuppressants[tiab] OR immunosuppressant[tiab] OR immunosuppression[tiab] OR immunosuppressions[tiab] OR steroids[mesh] OR steroid*[tiab] OR analgesics[mesh] OR analgesics[Pharmacological Action] OR analgesic[tiab] OR analgesics[tiab] OR anesthetics[mesh] OR "Anesthetics"[Pharmacological Action] OR anesthetic[tiab] OR anesthetics[tiab] OR "Vasodilator Agents"[Mesh] OR "Vasodilator Agents"[Pharmacological Action] OR vasodilator[tiab] OR vasodilators[tiab] OR vasorelaxants[tiab] OR vasorelaxant[tiab] OR "vasoactive antagonists"[tiab] OR "vasoactive antagonist"[tiab] OR "Cardiotonic Agents"[Mesh] OR "Cardiotonic Agents"[Pharmacological Action] OR cardiotonic[tiab] OR inotrope*[tiab] OR "cardiac stimulants"[tiab] OR "cardiac stimulant"[tiab] Or cardiotonic*[tiab] OR "myocardial stimulant*"[tiab] OR "cardioprotective agent*"[tiab] OR "Hypoglycemic Agents"[mesh] OR "Hypoglycemic Agents"[Pharmacological Action] OR "hypoglycemic agent*"[tiab] OR antihyperglycemic*[tiab] OR "hypoglycemic drug*"[tiab] OR antidiabetic*[tiab]	4165698
5	2000- and English	1437
	#5 AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR “clinical trial”[tiab] OR “clinical trials”[tiab] OR "evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tiab] OR evaluation studies[tiab] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case-control studies"[MeSH Terms] OR "case-control"[tiab] OR "cohort studies"[MeSH Terms] OR cohort[tiab] OR "longitudinal studies"[MeSH Terms] OR "longitudinal”[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tiab] OR "follow up"[tiab] OR "comparative study"[Publication Type] OR "comparative study"[tiab] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[mh] NOT humans[mh])	1056

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