Cardiology in the Young

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A systematic review of the evidence supporting post-operative medication use in congenital heart disease

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Review

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Abstract

Background: Targeted drug development efforts in patients with CHD are needed to standardise care, improve outcomes, and limit adverse events in the post-operative period. To identify major gaps in knowledge that can be addressed by drug development efforts and provide a rationale for current clinical practice, this review evaluates the evidence behind the most common medication classes used in the post-operative care of children with CHD undergoing cardiac surgery with cardiopulmonary bypass. *Methods:* We systematically searched PubMed and EMBASE from 2000 to 2019 using a controlled vocabulary and keywords related to diuretics, vasoactives, sedatives, analgesics, pulmonary vasodilators, coagulation system medications, antiarrhythmics, steroids, and other endocrine drugs. We included studies of drugs given post-operatively to children with CHD undergoing repair or palliation with cardiopulmonary bypass. *Results:* We identified a total of 127 studies with 51,573 total children across medication classes. Most studies were retrospective cohorts at single centres. There is significant age- and disease-related variability in drug disposition, efficacy, and safety. *Conclusion:* In this study, we discovered major gaps in knowledge for each medication class and identified areas for future research. Advances in data collection through electronic health records, novel trial methods, and collaboration can aid drug development efforts in standardising care, improving outcomes, and limiting adverse events in the post-operative period.

CHD is the most common birth defect with an incidence of 75 per 1000 live births and a prevalence of more than 2 million patients in the United States of America, excluding bicuspid aortic valves.[1,2] Many children will require surgical repair in infancy and early childhood with younger and more complex patients surviving hospital discharge due to advances in diagnosis, monitoring, and surgical and perfusion techniques.[3–6] Post-operative care has also improved with advances attributed to modifying factors such as case volume and creating dedicated pediatric cardiac ICUs.[4,7,8]

Advances in drug development in this population have not kept pace, leading to a paucity of dosing guidance, as well as safety and efficacy standards.[5,6,9–12] A lack of clear medication guidelines leaves treatment decisions up to clinical experience, findings from small observational studies, and extrapolation from adult data rather than relying on robust clinical trial evidence.[13,14] This exponentiates variation in post-operative medical management, and the lack of definitive data to support medication use puts children at risk for adverse events and denies them potential therapeutic benefits.[15–17] Clear medication guidelines may help minimise practice variation and ultimately improve the quality of care these children receive.

Drug trials in critically ill infants and children with CHD are challenging due to a limited number of eligible patients and the need to address substantial pathophysiologic and age-related variability in drug disposition, efficacy, and safety.[9,14,18,19] Legislative and scientific initiatives in the United States of America, such as the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, and in Europe, such as requirement of the Pediatric Investigation Plan, have encouraged paediatric drug development, but have had limited success in the CHD population.[9,20] This lack of success may be due to a limited ability to extrapolate adult efficacy data, necessitating population-specific trials, which are challenging to conduct.[5,11] Recently, the United States of America Food and Drug Administration has recognised the benefit of real-world data collected routinely from a variety of sources, such as the electronic health record, to generate real-world evidence that can guide clinical practice.[21] While randomised controlled trials remain the gold standard, practical approaches using RWD to generate RWE in the CHD population can inform targeted drug development efforts.[22–24]

In combination, these efforts will lead to more robust evidence, which may inform medication use guidelines and clinical practice.

In order to identify major gaps in knowledge that can be addressed by drug development efforts and provide a rationale for current clinical practice, we aim to systematically evaluate the evidence behind the most common medication classes used post-operatively in children with CHD undergoing surgery with cardiopulmonary bypass. We intend this article to serve as a broad overview with in-depth analyses of each medication class provided in subsequent articles.

Methods

Search strategy

We searched PubMed and EMBASE (2000–2019) to identify papers that studied medication use in the post-operative period in children with CHD undergoing cardiopulmonary bypass. Search terms were developed in conjunction with a Duke University Medical Center librarian. We defined our patient population by using a controlled vocabulary and keywords related to *post-operative care, heart surgery,* and *cardiopulmonary bypass* in the *paediatric* population (birth to 18 years). We then searched this population for each medication class: "steroid," "diuretic," "anticoagulant OR thrombin inhibitor," "analgesics OR sedation," "anesthetics," "vasodilator agents OR vasorelaxant," "cardiotonic agent OR inotrope OR cardiac stimulants," "hypoglycemic agent OR insulin OR thyroid OR calcium," "anti-arrhythmia agents OR antiarrhythmic." Animal studies, pre- or intra-op medication administration, studies in languages other than English, and case reports, letters, editorials, and comments were excluded. The search strategies are shown in the Appendix. References from searched articles were also considered and cited if they met the aforementioned criteria.

Study selection

The final search results were compiled and imported into EndNote (Clarivate Analytics, Philadelphia, PA, United States of America). Studies were deemed eligible if they focused on medication administration in the post-operative period for children undergoing cardiopulmonary bypass. Two reviewers independently screened and reviewed titles and study abstracts to assess their eligibility. Full-text articles were retrieved if the abstract provided insufficient information to establish eligibility or if the article passed the first eligibility screening.

Data extraction and synthesis

A standardised data collection form was used to extract the relevant data from each eligible study. The following data were collected: key characteristics of the study (e.g. study year, study design), characteristics of the study population (e.g. age, cardiac defect), intervention, and findings.

Results

Our literature search resulted in 2594 studies across all medication classes, of which 127 met inclusion criteria. This included 9 diuretic studies, 31 vasoactive studies, 13 sedative studies, 14 analgesic studies, 15 antiarrhythmic studies, 24 studies regarding pulmonary vasodilators, 7 studies about the coagulation system, 10 steroid studies, and 4 studies about other endocrine drugs. A total of 51,573 patients were included in these studies over the 19-year time period.

Diuretics

Out of the 110 records retrieved by the systematic search in PubMed and EMBASE, 9 studies met the inclusion criteria and included a total of 624 patients (Table 1). There were five retrospective studies, two prospective randomised controlled studies, one open-label prospective study, and one *post hoc* analysis of a randomised controlled study.[25–33] Medications included in these studies were loop diuretics (furosemide [89%], ethacrynic acid [22%]), vasopressin antagonists (tolvaptan [22%]), aldosterone antagonists (spironolactone [22%]), carbonic anhydrase inhibitors (acetazolamide [11%]), and methylxanthines (aminophylline [11%]).

All included studies were single centre and at least partly studied furosemide. While electrolyte abnormalities were described, such as hypokalaemia or metabolic alkalosis, all medications studied were safe with regard to haemodynamics. Furosemide pharmacokinetics has been studied in children, but there continues to be a lack of consensus on the nuances of dosing in the post-cardiopulmonary bypass setting, particularly regarding intermittent versus continuous diuretic infusion, and whether to start at higher doses of diuretic and titrate down, or start low and increase the dose. Response to diuretics also may predict outcomes – two studies showed that children who responded to diuretics were less likely to develop post-operative morbidities, such as acute kidney injury, fluid overload >15%, and need for peritoneal dialysis, prolonged mechanical ventilation, and prolonged hospitalisation – although the response to diuretics is likely confounded by several operative and post-operative characteristics.[26,32] Some studies suggest that ethacrynic acid may be a better alternative to furosemide in obtaining negative fluid balance with less drug.[27,28] Medications such as acetazolamide or tolvaptan may be beneficial to augment diuretic effects post-operatively.[31–33] There are a lack of multicentre randomised trials to determine optimal dosing and efficacy of post-operative diuretics.

Vasoactives

Overall, 423 records retrieved by the systematic search in PubMed and EMBASE, 31 studies met the inclusion criteria and included a total of 1866 children (Table 2).[34–64] Due to different pharmacologic properties, we classified vasoactive medications into two groups: inotropes and systemic vasodilators.

Inotropes

There were a total of 26 inotrope studies that included 1467 children.[34–48,51–61] All but two studies were single centre. There were nine retrospective cohort studies; nine prospective, randomised, blinded studies; five prospective open-label studies; and three prospective observational studies. Three studies included a placebo arm. Inotropes included in these studies were adrenergic modulators (dobutamine [12%], docarpamine [4%], epinephrine [4%], dopamine [4%]), vasopressin (31%), calcium modulators (levosimendan [35%]), cyclic guanosine monophosphate modulators (nesiritide [3%]), and cyclic adenosine monophosphate modulators (milrinone [42%]).

The optimal dose for these medications remains unknown: only 48% of children were in the therapeutic range with milrinone, and

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Table 1. Characteristics of post-operative diuretic studies and study populations

Authors	Study design	Year studied	Primary intervention	n	Study population	Findings
van der Vorst et al[25]	Prospective open-label, single centre		Continuous furosemide Intravenous 0.1 mg/kg/hour starting dose	12	<12 months Clinical signs of volume overload and requiring inotropic support	Well tolerated Nine children required an increase in rate to 0.2 mg/kg/hour on POD2, consider starting at a higher dose and titrate down Effect of furosemide on urine output increases with decreasing creatinine
Borasino et al[26]	Retrospective cohort, single centre	2012–2015	Furosemide Intravenous 0.8–1.4 mg/kg	90	<90 days	UOP response to furosemide after bypass predicted peak fluid overload of >15%, and prolonged mechanical ventilation, PD, and hospitalisation
Ricci et al[27]	Prospective randomised, double-blind, controlled, single centre	2012–2013	Continuous furosemide versus ethacrynic acid Intravenous 0.2 mg/kg/hour furosemide equivalent starting dose	74	<12 months Clinical signs of fluid overload	Shorter time to negative fluid balance and higher cardiac index with ethacrynic acid compared to furosemide 30% less diuretic was needed with ethacrynic acid to achieve a similar urine output Hypokalaemia (91 episodes with furosemide, 88 episodes with ethacrynic acid) and metabolic alkalosis (70% of furosemide, 74% of ethacrynic acid) were frequent in both groups Both furosemide and ethacrynic acid were safe in terms of renal function
Haiberger et al[28]	*Post hoc* analysis of prospective randomised, double-blind, controlled, single centre	2012–2013	Continuous furosemide versus ethacrynic acid Intravenous 0.2 mg/kg/hour furosemide equivalent starting dose	67	<12 months Clinical signs of fluid overload	Infants require higher diuretic doses with less urine output in the early post-operative period Increased cross-clamp time was associated with higher diuretic dose Blood pH at the end of POD0 was associated with lower diuretic dose
Onder et al[29]	Retrospective cohort, single centre	2007–2013	Aminophylline versus furosemide Intravenous Furosemide 1 mg/kg/dose Aminophylline 5 mg/kg/dose	200	<21 years Intraoperative oliguria	Intraoperative aminophylline increased urine output at 8 hours compared to intraoperative furosemide, but this effect was not maintained at 48 hours Elevated CVP was associated with increased risk of AKI, death, and need for RRT, but aminophylline was protective against these outcomes
Kwiatkowski et al[30]	Prospective randomised unblinded controlled, single centre	2011–2015	PD versus furosemide Intravenous 1 mg/kg/dose every 6 hours starting dose	73	<6 months Post-operative oliguria	No difference in obtaining a net negative fluid balance on POD1 between PD and furosemide PD had less prolonged mechanical ventilation, fewer inotropic requirements, and fewer electrolyte abnormalities
Katayama et al[31]	Retrospective cohort, single centre	2013–2016	Furosemide + spironolactone +/−tolvaptan Enteral Tolvaptan 0.45 mg/kg/dose Furosemide 0.67–1 mg/kg/dose every 8 hours Spironolactone 0.67–1 mg/kg/dose every 8 hours	43	<18 years Simple congenital left-to-right shunts	A single dose of tolvaptan in addition to furosemide and spironolactone led to higher cumulative urine output, less of a decrease in CVP, and required less additional intravenous diuretic doses compared to those receiving furosemide and spironolactone alone

(*Continued*)

Table 1. (*Continued*)

Authors	Study design	Year studied	Primary intervention	n	Study population	Findings
Kerling et al[32]	Retrospective cohort, single centre	2011–2017	Tolvaptan Enteral 1 mg/kg/day	25	<24 months Diuretic refractory capillary leak syndrome	Those who responded to tolvaptan had greater weight reduction, earlier weaning from ventilator, and shorter time in the ICU Serum sodium and osmolality increased over time
Lopez et al[33]	Retrospective cohort, single centre	2010–2011	Acetazolamide + spironolactone + furosemide +/− thiazide Enteral Acetazolamide 5–10 mg/kg/dose every 12 hours	40	<18 years Post-operative metabolic alkalosis	Acetazolamide for post-operative metabolic alkalosis increased urine output and decreased diuretic requirement

AKI = acute kidney injury; CVP = central venous pressure; PD = peritoneal dialysis; POD = post-operative day; RRT = renal replacement therapy; UOP = urine output

there was patient variability over time.[44] A prospective, double-blind, placebo-controlled, multiple-arm, multicentre trial of different milrinone dosing regimens suggest high-dose milrinone is associated with reduced risk of low cardiac output syndrome in children with biventricular repairs, although other studies have shown the need for higher inotropic support with high-dose milrinone in children with pulmonary hypertension.[41,45] The nuances of disease-specific alterations in drug disposition make general dosing guidelines difficult, possibly support age- and disease-specific dosing guidelines, and highlight the need for studies to uncover what drives variability in drug disposition. Levosimendan appears to have some beneficial effects including improved cardiac output and lower heart rates, when compared to other inotropes, such as milrinone or dobutamine,[51,52,54] However, other endpoints, such as lactate, central venous pressure, and LCOS, showed no difference between medications.[53,56] There is conflicting evidence regarding the association of inotropic medications and tachyarrhythmias.[45,48,60]

The majority of studies used mean arterial pressure, central venous pressure, and lactate as endpoints to evaluate the efficacy of vasoactive medications. Other endpoints were studied, such as occurrence of LCOS, but varied widely, which makes comparisons across studies difficult. While there were some studies that evaluated different dosing regimens and compared one or two inotropes, there continues to be a lack of validated endpoints for evaluating inotropic efficacy and a lack of multicentre randomised controlled trials comparing different classes of inotropes.

Systemic vasodilators

There were a total of 5 studies of systemic vasodilators that met inclusion criteria and included 399 children.[49,50,62–64] All studies were single centre. Four studies were retrospective cohort studies, and one study was a prospective observational study. Medications included in these studies were adrenergic modulators (phenoxybenzamine [20%], phentolamine [20%]), calcium channel blockers (nicardipine [20%]), and cyclic guanosine monophosphate modulators (nesiritide [20%], nitroprusside [40%]).

Systemic vasodilators are used to manage hypertension in the post-operative period. Most studies used a decrease in mean arterial pressure as an endpoint. Overall, the systemic vasodilators were well tolerated post-operatively. The most common side effects were hypotension, and nitroprusside led to toxic cyanide levels in 11% of children.[50] Only one study compared medications in this class, and no studies were multicentre.

Sedatives

Out of the 316 records retrieved by the systematic search in PubMed and EMBASE, 13 studies met the inclusion criteria and included a total of 726 children (Table 3).[65–77] All studies were single centre. There were four retrospective cohort studies; one retrospective case–control study; one prospective cohort study; two prospective open-label PK/pharmacodynamics studies, and two prospective, randomised controlled studies. All medications studied were alpha-2 adrenoreceptor agonists (dexmedetomidine [80%], clonidine [10%]) and benzodiazepines (midazolam [40%]). The majority of studies evaluated the use of sedatives in conjunction with an analgesic, such as an opioid.

Children receiving dexmedetomidine receive concomitant sedation or analgesic medications 98% of the time.[68] Dexmedetomidine may reduce the amount of concomitant benzodiazepine needed, but there is conflicting evidence if there is a

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Table 2. Characteristics of post-operative vasoactive studies and study populations including inotropes and systemic vasodilators

Inotropes						
Authors	Study design	Year studied	Primary intervention	n	Study population	Findings
Agrawal et al[34]	Prospective open-label, single centre	2008	AVP Intravenous 0.0005 U/kg/minute starting dose	12	<10 years old Refractory vasodilatory shock	Total inotrope requirement decreased after starting AVP MAPs increased significantly after starting AVP No changes in heart rate, UOP, bicarbonate, Na level Thrombocytopenia that resolved after stopping AVP was noted
Alten et al[35]	Retrospective cohort, single centre	2008–2010	AVP Intravenous 0.0003 U/kg/minute starting dose	37	<28 days Norwood or ASO	Less inotropic support in children receiving AVP Quicker to net negative fluid balance with AVP No difference in CVP, UOP, MAP, maximum lactate between groups, length of ventilation, or ICU stay Lower sodium with AVP
Burton et al[36]	Retrospective cohort, single centre	2007–2010	AVP Intravenous 0.0003 U/kg/minute starting dose	29	<28 days Refractory vasodilatory shock	Increase in UOP, PaO2, SBP, and CVP after start of AVP Decrease in serum lactate, PaCO2 with AVP Lower sodium in AVP group, 35% received at least one hypertonic saline infusion
Davalos et al[37]	Retrospective cohort, single centre	2009–2010	AVP Intravenous 0.0003–0.002 U/kg/minute	76	<6 years	Serum sodium decreased more quickly and to a greater extent in children receiving AVP, without serious adverse events Higher UOP, heart rate, serum lactate, and inotrope requirement in those receiving AVP
Lechner et al[38]	Retrospective cohort, single centre	2003–2005	AVP Intravenous 0.0001 U/kg/minute starting dose	17	3–12 days Refractory vasodilatory shock	Increase in systolic and diastolic blood pressure and UOP with AVP Decrease in inotrope requirement No change in sodium
Lu et al[39]	Retrospective cohort, single centre	2013–2015	AVP Intravenous 0.2–2 mcg/kg/minute	70	<15 years Vasodilatory shock	Increase in blood pressure at 2 hours after AVP initiation Decreased fluid requirement and lactate, increased UOP with AVP
Mastropietro et al[40]	Retrospective cohort, single centre	2009–2010	AVP Intravenous 0.3–2 U/kg/minute	34	≤6 years Haemodynamic instability	AVP led to hemodynamic improvement in 50% of children Later initiation, after the first post-operative night, was associated with haemodynamic improvement, likely related to endogenous AVP concentrations
Barnwal et al[41]	Prospective randomised, double-blind, single centre		Milrinone Intravenous Low-dose 0.375 mcg/kg/minute Medium dose 0.5 mcg/kg/minute High-dose 0.75 mcg/kg/minute	90	6 weeks–12 years Pulmonary hypertension	No difference in MAP, oxygenation index, or CVP between groups High-dose group needed higher inotropic support
Chu et al[42]	Prospective observational, single centre		Milrinone Intravenous Loading dose of 20 mcg/kg followed by 0.2 mcg/kg/minute	10	<6 months Tetralogy of Fallot and pulmonary hypertension	Decrease in PAP/SBP ratio 15 minutes after milrinone infusion that persisted during infusion

(*Continued*)

Table 2. (*Continued*)

Inotropes						
Authors	Study design	Year studied	Primary intervention	n	Study population	Findings
Duggal et al[43]	Prospective open-label, single centre	2001–2003	Milrinone Intravenous 0.3–0.6 mcg/kg/minute	15	0.2–16 months LCOS	Milrinone improved biventricular myocardial function
Garcia Guerra et al[44]	Prospective open-label, single centre	2007–2009	Milrinone Intravenous 0.5 mcg/kg/minute	63	≤2 years	Only 48% of children in the therapeutic range at standard dosing and there was within-patient variability over time
Hoffman et al[45]	Prospective double-blind, placebo-controlled, multiple-arm trial, multicentre		Placebo versus low-dose milrinone versus high-dose milrinone Intravenous Low-dose 25 mcg/kg bolus then 0.25 mcg/kg/minute over 35 hours High-dose 75 mcg/kg bolus then 0.75 mcg/kg/minute over 35 hours	238	<6 years Biventricular repair	High-dose milrinone was associated with reduced risk of LCOS No difference in thrombocytopenia in the groups, tachyarrhythmias were rare
Cavigelli-Brunner et al[46]	Prospective randomised, double-blind, single centre		Milrinone versus dobutamine Intravenous Milrinone 50 mcg/kg bolus followed by 0.75 mcg/kg/minute Dobutamine 6 mcg/kg/minute 24 hours	50	<15 years Risk of LCOS	Milrinone and dobutamine are equally effective in preventing LCOS Dobutamine required more sodium nitroprusside suggesting that milrinone promotes more systemic vasodilation
De Souza et al[47]	Prospective observational, single centre		Dobutamine Intravenous Low-dose 5 mcg/kg/minute High-dose 10 mcg/kg/minute	10	<8 years	Intramucosal pH increased in the high-dose group at 12 and 24 hours but was not statistically significant
Costello et al[48]	Prospective randomised, double-blind, placebo-controlled, multi-arm parallel-group, single centre	2007–2013	Milrinone versus nesiritide versus placebo Intravenous Milrinone 50 mcg/kg bolus followed by 0.5 mcg/kg/minute Nesiritide 2 mcg/kg bolus followed by 0.015 mcg/kg/minute	106	<16 years Fontan	Milrinone was frequently discontinued due to hypotension Arrhythmias were nearly twice as common in those receiving milrinone
Ebade et al[51]	Prospective randomised, open-label, single centre	2011–2012	Levosimendan versus dobutamine Intravenous Levosimendan 15 mcg/kg loading then 0.1–0.2 mcg/kg/minute Dobutamine 4–10 mcg/kg/minute	50	<3 years Septal defects and pulmonary hypertension	Both drugs reduced PAP and improved cardiac index PAP was lower and cardiac index was higher in children who received levosimendan compared to dobutamine

Table 2. (*Continued*)

Lechner et al[52]	Prospective randomised, double-blind, single centre	2007–2009	Levosimendan versus milrinone Intravenous Levosimendan 0.1 mcg/kg/minute Milrinone 0.5 mcg/kg/min	37	<12 months	No difference in cardiac index in the first 48 hours, inotrope requirement, or urine output Levosimendan had an increase in cardiac output over time while cardiac output remained stable for milrinone
Momemi et al[53]	Prospective randomised, double-blind, single centre	2008–2009	Levosimendan versus milrinone Intravenous Levosimendan 0.05 mcg/kg/minute Milrinone 0.4 mcg/kg/minute	36	<5 years	Levosimendan had lower rate pressure index (surrogate for myocardial oxygen demand) No difference in lactate levels
Pellicer et al[54]	Prospective randomised, double-blind, single centre	2009–2010	Levosimendan versus milrinone Intravenous Levosimendan 0.1 mcg/kg/minute increased to 0.2 mcg/kg/minute at 2 hours Milrinone 0.5 mcg/kg/minute increased to 1.0 mcg/kg/minute at 2 hours	20	<35 days	Milrinone had higher lactate, higher inotrope requirement, and lower pH at 6 hours, and higher inotrope requirement at 12 hours Levosimendan had lower heart rates
Amiet et al[55]	Retrospective cohort, single centre	2005–2013	Levosimendan Intravenous 0.1 mcg/kg/minute for 48 hours, then 0.2 mcg/kg/minute for 24 hours	62	<14 years LCOS	Diuresis, central venous oxygen saturation improved at 24 hours, lactate significantly decreased
Osthaus et al[56]	Retrospective cohort, single centre	2006–2007	Levosimendan Intravenous 12 mcg/kg loading dose followed by 0.2 mcg/kg/minute	7	<9 months High risk for LCOS	Lactate decreased and central venous oxygenation increased at 24 and 48 hours Levosimendan did not affect heart rate, MAP, or CVP
Ricci et al[57]	Prospective randomised, open-label, single centre	2008–2010	Levosimendan + standard inotropic support or standard inotropic support alone Intravenous 0.1 mcg/kg/minute	63	<30 days	Levosimendan had lower lactate levels and required less inotropes No difference in rates of LCOS
Thorlacius et al[58]	Prospective randomised, double-blind, controlled, multicentre	2014–2017	Levosimendan versus milrinone Intravenous Levosimendan 12 mcg/kg bolus then 0.1 mcg/kg/minute Milrinone 48 mcg/kg bolus then 0.4 mcg/kg/minute	71	≤12 months Tetralogy of Fallot, AVCD, or VSD	No difference in rates of acute kidney injury, inotropic support, lactate, or fluid overload
Wang et al[59]	Prospective randomised, double-blind, placebo-controlled, single centre	2018–2019	Levosimendan versus placebo Intravenous 0.05 mcg/kg/minute	187	<48 months old	No difference in duration of mechanical ventilation, LCOS, 90-day mortality No adverse events

(*Continued*)

Table 2. (*Continued*)

Inotropes						
Authors	Study design	Year studied	Primary intervention	n	Study population	Findings
McFerson et al[60]	Retrospective cohort, single centre	2008–2012	Dopamine, AVP, epinephrine, milrinone Intravenous Dopamine 0–10 mcg/kg/minute AVP 0–0.0012 U/kg/minute Epinephrine 0–0.5 mcg/kg/minute Milrinone 0.5–1.0 mcg/kg/minute	66	<30 days Norwood	50% of children had post-operative tachyarrhythmias Higher doses of milrinone and longer duration of epinephrine was associated with tachyarrhythmias
Watarida et al[61]	Prospective observational, single centre		Docarpamine while weaning dopamine Enteral 40 mg/kg every 8 hours	11	Children	Dopamine was able to be weaned from 5 mcg/kg/minute to off in 8 hours Mean right atrial pressures decreased 4 hours after docarpamine administration Mixed venous saturation increased after docarpamine No changes in heart rate, systolic or diastolic blood pressure
Systemic vasodilators						
Author	Study design	Year studied	Primary intervention	n	Study population	Findings
Simsic et al[49]	Prospective observational, single centre		Nesiritide Intravenous 1 mcg/kg followed by 0.01 mcg/kg/minute × 6 hours then 0.02 mcg/kg/minute × 18 hours	17	<15 years	MAP decreased by 7% after loading dose No significant haemodynamic compromise
Moffett et al[50]	Retrospective cohort, single centre	2002	Nitroprusside Intravenous 0.1–4.1 mcg/kg/minute	63	<19 years	Toxic cyanide levels were found in 11% of children Mean dose of nitroprusside is the best predictor of elevated cyanide levels
Stone et al[62]	Retrospective cohort, single centre	2010–2015	Nicardipine Intravenous 0.5 mcg/kg/minute starting dose	68	<18 years Post-operative hypertension	13% of children had hypotension No difference in blood pressure, length of stay, or duration of mechanical ventilation in children <6 months or >6 months
Furck et al[63]	Retrospective cohort, single centre	1996–2007	Nitroprusside versus phentolamine Intravenous Nitroprusside 1.5–2 mcg/kg/minute Phentolamine 0.9 mcg/kg/minute	146	<60 days Norwood	Phentolamine had lower MAP and coronary perfusion pressure compared to nitroprusside
De Oliviera et al[64]	Retrospective cohort, single centre	1996–2002	Phenoxybenzamine Intravenous 0.25 mg/kg loading then 0.5–1 mg/kg for 24 hours	105	<6 months Norwood	Phenoxybenzamine was associated with a decrease in sudden circulatory collapse

ASO = arterial switch operation; AVCD = atrioventricular canal defect; AVP = arginine vasopressin; CVP = central venous pressure; LCOS = low cardiac output syndrome; MAP = mean arterial pressure; PAP = pulmonary artery pressure; SBP = systolic blood pressure; UOP = urine output; VCD = ventricular septal defect

Table 3. Characteristics of post-operative sedative studies and study populations

Authors	Study type	Year studied	Primary intervention	n	Study population	Findings
Chrysostomou et al[65]	Retrospective cohort, single centre	2004–2007	DEX versus DEX + sedatives/ analgesics versus DEX + fentanyl + sedatives/ analgesics Intravenous DEX 0.1–1.25 mcg/kg/hour	80	<12 months	Fentanyl did not decrease DEX dose, no change in rescue meds needed No difference in DEX dose between intubated or extubated children Infants require higher doses than neonates Pain, sedation, SBP, and ABGs were similar between groups
Garisto et al[66]	Prospective randomised, open-label, controlled, single centre	2012–2015	DEX + opioid + benzodiazepine versus opioid + benzodiazepine Intravenous DEX 0.5 mcg/kg/hour	48	1–24 months	No difference in haemodynamics between the two groups No difference in length of mechanical ventilation Less withdrawal symptoms with DEX
Hasegawa et al[67]	Retrospective cohort, single centre	2011–2013	DEX + midazolam versus midazolam Intravenous DEX 0.4–0.6 mcg/kg/hour	40	<12 months VSD	DEX reduces concomitant midazolam, heart rate, and lactate levels No adverse events with DEX
Horvath et al[68]	Retrospective cohort, single centre	2010–2011	DEX Intravenous 0.12–2 mcg/kg bolus then 0.1–2.2 mcg/kg/hour	107	<18 years	98% received a concomitant medication (opioid, benzos) Adverse events of bradycardia and hypotension were associated with higher bolus doses (1 mcg/kg versus 0.2 mcg/kg) No significant difference in children with trisomy 21 Older infants receive higher doses than neonates (0.77 versus 0.56 mcg/kg/hour) Can have withdrawal if infusion >72 hours
Hosokawa et al[69]	Prospective cohort, single centre	2006–2007	DEX versus standard sedation Intravenous 0.4–0.6 mcg/kg/hour	141	≤15 years	DEX resulted in adequate sedation and shorter time to extubation DEX had more bradycardia and hypotension but less respiratory events
Kleiber et al[70]	Retrospective cohort, single centre	2011–2013	Clonidine versus clonidine + opioid Intravenous Clonidine 2 mcg/kg loading dose then 0.5 mcg/kg/hour	23	<2 months	Clonidine was haemodynamically tolerated, consider as an alternative to midazolam
Potts et al[71]	Prospective open-label, single-centre PD analysis		DEX Intravenous 1–4 mcg/kg single dose over 10 minutes	29	≤14 years	Single bolus dose produces a biphasic effect on MAP: there is an initial and transient increase in MAP with the bolus dose related to high plasma concentrations than a delayed decrease in MAP when the drug reaches the central nervous system
Prasad et al[72]	Prospective randomised, double-blind, controlled, single centre		DEX versus fentanyl Intravenous DEX 0.5 mcg/kg/hour Fentanyl 1 mcg/kg/hour	60	1–14 years	Similar levels of sedation and haemodynamics Earlier extubation after stopping infusion with DEX

(*Continued*)

Table 3. (*Continued*)

Authors	Study type	Year studied	Primary intervention	n	Study population	Findings
Su et al[73]	Prospective, open-label dose escalation PK/PD study	2004–2006	DEX Intravenous Low dose: 0.35 mcg/kg loading dose then 0.25 mcg/kg/hour Medium dose: 0.7 mcg/kg loading dose then 0.5 mcg/kg/hour High dose: 1 mcg/kg loading dose then 0.75 mcg/kg/hour	32	1–24 months	97% of children were able to be extubated while on DEX No significant haemodynamic or respiratory alterations in the dose range DEX provides adequate sedation while reducing supplemental analgesic requirements
Tokuhira et al[74]	Retrospective cohort, single centre	2003–2006	DEX versus standard sedation Intravenous 0.1–1 mcg/kg/hour	14	≤14 years Fontan	DEX caused the need for pacing (HR < 90) than the standard sedation regimen DEX had no evidence of increase partial pressure of arterial carbon dioxide compared to the control group There was no significant difference in hypotensive events in the two groups Serum lactate levels were reduced in the DEX group
Kleiber et al[75]	Retrospective case–control, single centre	2011–2013	Pre-emptive midazolam versus targeted sedation Intravenous Midazolam 60 mcg/kg/hour	66	<6 months	Routine sedation may not prevent LCOS, targeted sedation did not compromise haemodynamic stability and may reduce sedative exposure
Penk et al[76]	Prospective randomised, open-label, controlled, single centre	2014–2016	Intermittent morphine and midazolam versus continuous + intermittent morphine and midazolam Intravenous Midazolam 0.05 mg/kg every hour or 0.03 mg/kg/hour Morphine 0.05 mg/kg every 2 hours or 0.03 mg/kg/hour	60	3 months – 4 years	No difference in sedation or pain scores or total amount of bolus doses required Continuous and intermittent dosing resulted in higher total amount of medication received, longer hospital length of stay, and more positive fluid balance
Rigby-Jones et al[77]	Prospective cohort, single centre	2003–2005	Midazolam and remifentanil Intravenous Midazolam 50 mcg/kg/hour Remifentanil 0.8 mcg/kg/minute	26	<10 years	Younger and smaller children require higher remifentanil infusion rates due to enhanced clearance rates This combination provides satisfactory sedation

DEX = dexmedetomidine; LCOS = low cardiac output syndrome; MAP = mean arterial pressure; PD = pharmacodynamics; PK = pharmacokinetics; VSD = ventricular septal defect

reduction in the amount of concomitant sedation or length of mechanical ventilation.[66–68,72,73] Multiple studies showed that infants require higher doses than neonates.[68,78] These medications were well tolerated as continuous infusions, but higher dose boluses led to hypotension and bradycardia, and long-term (>72 hours) exposure led to withdrawal.[68] One study related sedation to clinical outcomes (LCOS) and showed that pre-emptive midazolam did not prevent LCOS, but that targeted use of midazolam may reduce total sedative exposure.[75] While intraoperative anaesthetics, particularly volatile agents, have been linked to lower neurodevelopmental outcome scores in children undergoing cardiopulmonary bypass, there is a paucity of data regarding anaesthetic or sedative management in the post-operative period and how this may be related to long-term outcomes.[79]

Analgesics

Out of the 308 records retrieved by the systematic search in PubMed and EMBASE, 14 studies met the inclusion criteria and included a total of 1672 children (Table 4). All but one study was single centre. There were seven retrospective cohort studies; two prospective PD studies; two retrospective case–control studies; two prospective, randomised studies; and one *post hoc* analysis of a prospective observational cohort study.[80–93] Medications included in these studies were opioids (morphine [43%], fentanyl [29%], hydromorphone [7%], remifentanil [7%]), and non-steroidal anti-inflammatory drugs (ketorolac [36%], acetaminophen [7%]).

Opioid medications are well tolerated with the most common side effects being vomiting, pruritus, and (rarely) respiratory depression.[82,83,87] Fentanyl is the most commonly prescribed opioid post-operatively used in as many as 90% of patients.[84] There is wide dose variation in children to achieve optimal pain management, and most children receive concomitant sedative medications.[80–84] Two studies studied the effect of opioid medication in children with Down syndrome and found no difference in opioid requirements for those with Down syndrome compared to those without, with no difference in PK or PD.[85,86] Ketorolac is a non-steroidal anti-inflammatory drug that is used as an adjunct for post-operative pain control. Multiple studies found no increase in adverse renal or haematologic events except when ketorolac was administered in conjunction with aspirin, even in children <6 months old, although there was evidence of platelet dysfunction.[88–92] In addition to pain control, acetaminophen may be protective against acute kidney injury.[93]

Antiarrhythmics

Out of the 96 records retrieved by the systematic search in PubMed and EMBASE, 15 studies met the inclusion criteria and included a total of 1744 children (Table 5).[78,94–107] All studies were single centre. There were nine retrospective cohort studies and one retrospective case–control study. The other five were prospective: one randomised, two randomised, and placebo-controlled, one case-controlled, and one observational. Medications included were potassium channel blockers (amiodarone [40%]), sodium channel blockers (flecainide [7%]), alpha 2 adrenoreceptor agonists (dexmedetomidine [27%]), selective beta 1 adrenoreceptor antagonists (landiolol [27%]), and magnesium (7%).

Overall, amiodarone was well tolerated, significantly decreased the rate and severity of junctional ectopic tachycardia, and improved haemodynamics in post-operative children whether used as prophylaxis or treatment.[94–98] Similarly, a study of flecainide showed efficacy without adverse events in 7/7 cases.[100] Landiolol shows promise for the treatment of tachyarrhythmias with rare adverse events.[103–106] Dexmedetomidine, while typically used as a sedative, has also been studied in preventing tachyarrhythmias. Evidence is conflicting regarding its efficacy for treating tachyarrhythmias.[78,99,102] However, dexmedetomidine is also known to cause bradyarrhythmias in a dose-dependent fashion.[99,102]

Because of the generally low incidence of post-operative arrhythmias, quality studies to provide conclusive evidence for medication use are challenging. However, post-operative arrhythmias can lead to haemodynamic instability, longer ICU stays, longer hospitalisations, and increased mortality.[100] Therefore, studies should continue to evaluate the efficacy, optimal dosing regimen, and adverse events in the post-cardiopulmonary bypass population through multisite, longitudinal pragmatic trials.

Pulmonary vasodilators

Out of the 271 records retrieved by the systematic search in PubMed and EMBASE, 24 studies met the inclusion criteria and included a total of 40,960 children (Table 6).[108–131] The majority of studies were prospective (63%), and two trials were multicentre (8%). Medications included were inhaled nitric oxide (50%), inhaled prostacyclin analogs (iloprost [21%]), phosphodiesterase inhibitors (sildenafil [33%], milrinone [8%]), and endothelin receptor antagonists (BQ123 [4%]).

Due to its delivery, inhaled nitric oxide acts locally without systemic effects,[117] decreasing mean pulmonary artery pressures at low doses, without further effect at higher doses.[108] In addition, inhaled nitric oxide has been associated with a shorter duration of mechanical ventilation and ICU stays, with decreased mortality for those with severe pulmonary hypertension.[108–110,113–116] Several smaller studies showed shorter hospital stays with inhaled nitric oxide, although a large retrospective cohort found that inhaled nitric oxide was associated with an increased length of hospital stay.[111,112] Inhaled nitric oxide in combination with other medications may have an additive effect.[117,118] Iloprost is appealing because it can be administered via inhalation; however, studies have shown unfavourable haemodynamics and pulmonary congestion.[119–123] Systemic medications such as sildenafil and BQ123 lower pulmonary vascular resistance, but also cause systemic effects such as hypotension.[127–131]

Pulmonary hypertension is a significant post-operative complication that can have high mortality.[113] Nevertheless, large prospective studies in this population are difficult to complete, as evidenced by a multicentre randomised, double-blind, placebo-controlled trial evaluating three doses of intravenous sildenafil in children <17 years for the treatment of post-operative pulmonary hypertension that terminated early due to slow patient accrual.[127] Novel trial designs are needed to improve post-operative outcomes.

Coagulation system

Out of the 383 records retrieved by the systematic search in PubMed and EMBASE, 7 studies met the inclusion criteria and included a total of 1297 children (Table 7).[132–138] All studies were single centre. There were three retrospective cohort studies; one prospective observational study; one prospective cohort with historical controls; and two prospective, randomised controlled studies. Medications included were vitamin K antagonists (warfarin [43%]), thromboxane inhibitors (aspirin [14%]), factor Xa inhibitors (heparin [29%]), and fibrinogen concentrate (14%).

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Table 4. Characteristics of post-operative analgesic studies and study populations

Authors	Study type	Year studied	Primary intervention	n	Study population	Findings
Bueno et al[80]	Retrospective cohort, single centre	2001–2005	Continuous fentanyl, intermittent morphine or dipyrone Intravenous Fentanyl 2–3 mcg/kg/hour Morphine 0.08 mg/kg Dipyrone 24.4 mg/kg	30	<28 days	80% received continuous analgesia with fentanyl Most infants had significant dose variation in fentanyl dose 70% received concomitant sedation Continuous administration is preferred as it reduces variation in serum concentration
Elkomy et al[81]	Prospective open-label, single-centre PD analysis		Morphine Intravenous Loading 0.15 mg/kg then 0.02 mg/kg to increase by 0.01 mg/kg as needed by NCA	20	<6 years Two ventricles	Morphine doses >0.1 mg/kg did not increase tolerable pain durations Time to remedication is a useful endpoint for assessing analgesia
Iodice et al[82]	Retrospective cohort, single centre	2006–2007	Morphine via PCA or NCA Intravenous 10–30 mcg/kg/hour and 50 mcg/kg boluses as needed	54	6 months–18 years Fast track management	Median infusion time was 29 hours 89% of children also received paracetamol and NSAIDs Side effects of pain regimen included vomiting (42%) and itching (2%), no cases of respiratory depression
Naguib et al[83]	Retrospective cohort, single centre	2008–2011	Fentanyl Intravenous 0.5 mcg/kg by NCA +/− basal rate of 0.5 mcg/kg/hour and naloxone 0.25 mcg/kg/hour	33	≤90 days Hybrid stage 1 for HLHS	Children extubated in the OR has shorter courses of fentanyl use 15% of children received concomitant DEXmedetomidine and required less fentanyl Adverse events noted in 9% of children: pruritis, excessive sedation, respiratory depression
Naguib et al[84]	Retrospective cohort, single centre	2008–2011	Fentanyl, morphine, hydromorphone Intravenous Fentanyl 0.5 mcg/kg NCA +/− 0.5 mg/kg/hour Morphine 20 mcg/kg NCA + 20 mcg/kg/hour Hydromorphone 4 mcg/kg + 4 mcg/kg/hour	57	<15 months CS2 or bidirectional Glenn for HLHS	Fentanyl was the most commonly prescribed opioid (95%) Children undergoing CS2 had higher opioid requirements than those undergoing Glenn
Valkenburg et al[85]	Prospective observational, single-centre PK/PD study	2012	Morphine PK/PD in Down syndrome Intravenous Loading dose 100 mcg/kg then 40 mcg/kg/hour	38	≤36 months	No evidence that PK or PD is different for morphine in Down's children
Van Driest et al[86]	Retrospective cohort, single centre		Standard of care opioid regimen Intravenous 0.1 mg/kg/hour morphine dose equivalents	121	≤17 years	No difference in cumulative opioid doses in the first 24 hours post-operatively or in the first 96 hours post-operatively between those with Down syndrome and those without Age, bypass time, benzodiazepines, neuromuscular blockade were associated with higher opioid doses

Table 4. (*Continued*)

Xiang et al[87]	Prospective randomised, single centre	2011–2012	Remifentanil versus fentanyl NCA Intravenous Remifentanil 0.07 mcg/kg/minute with 0.25 mcg/kg boluses Fentanyl 0.1 mcg/kg/minute with 1 mcg/kg bolus dose	50	1–3 years Simple septal defects	Similar pain control but remifentanil had fewer adverse events
Dawkins et al[88]	Retrospective case–control, single centre	2004–2007	Ketorolac Intravenous 0.4–0.63 mg/kg every 6–8 hours	38	<6 months	No difference in renal impairment or haematologic complications Ketorolac did not decrease standard analgesic use
Gupta et al[89]	Prospective randomised, single centre	2003	Standard of care +/− ketorolac Intravenous 0.5 mg/kg/dose every 6 hour	70	<16 years	No increased risk of bleeding complications with ketorolac
Kim et al[90]	*Post hoc* analysis of prospective observational, single centre	2014–2015	Ketorolac Intravenous	53	<17 years	All who received ketorolac had platelet dysfunction by TEG with platelet mapping compared to 8% of those who did not
Moffett et al[91]	Retrospective case–control, single centre	2007–2011	Ketorolac Intravenous Mean 0.48 mg/kg/dose in cases versus 0.49 mg/kg/dose in controls	56	<6 months	Risk factors for AKI included concomitant use of ketorolac and aspirin, and undergoing bidirectional Glenn procedure
Moffett et al[92]	Retrospective cohort, single centre	2005	Ketorolac Intravenous Mean 0.4 mg/kg/dose every 6 hours	53	<6 months	Ketorolac was not associated with any adverse renal or haematologic effects Ketorolac was effective for moderate post-operative pain control
Van Driest et al[93]	Retrospective cohort, multicentre	2008–2016	Acetaminophen Intravenous, enteral, or rectal Low total dose < 40 mg/kg Moderate total dose 40–80 mg/kg High total dose > 80 mg/kg	999	28 days–18 years	Lower incidence of AKI with any acetaminophen Cumulative dose-dependent reduction in AKI

AKI = acute kidney injury; CS2 = comprehensive stage 2; HLHS = hypoplastic left heart syndrome; NCA = nurse-controlled analgesia; NSAIDs = non-steroidal anti-inflammatory drugs; PCA = patient-controlled analgesia; TEG = thromboelastography

Table 5. Characteristics of post-operative antiarrhythmic studies and study populations

Authors	Study Design	Year studied	Primary intervention	n	Study population	Findings
Amrousy et al[94]	Prospective randomised, single centre	2011–2015	Prophylactic amiodarone versus placebo Intravenous 5 mg/kg loading dose then 10–15 mcg/kg/minute	117	≤24 months	Prophylactic amiodarone decreased the incidence and severity of JET and shortened ICU and hospital stay No significant adverse events with prophylactic amiodarone
Haas and Camphausen[95]	Retrospective cohort, single centre	1995–2005	Amiodarone Intravenous 5 mg/kg loading dose then 10–20 mg/kg/day infusion	71	<15 years JET	After 1 hour, there was a significant decrease in heart rate, increase in blood pressure, and decrease in filling pressures Amiodarone allowed catecholamine dose to be decreased
Imamura et al[86]	Retrospective case–control, single centre	2005–2009	Prophylactic amiodarone versus control Intravenous 2 mg/kg/day infusion	63	≤14 months Tetralogy of Fallot	Prophylactic amiodarone was associated with less JET No adverse events from amiodarone
Kovacikova et al[97]	Prospective cohort, single centre	1998–2007	Amiodarone Intravenous 2 mg/kg loading dose then 10–15 mcg/kg/minute	40	≤12 years JET	Amiodarone as first line treatment was effective in 45% of children Failure was associated with higher arteriovenous oxygen saturation difference and lower body temperature
Laird et al[98]	Retrospective cohort, single centre	1992–2000	Amiodarone Intravenous 5 mg/kg loading dose then 10–20 mg/kg/day infusion	11	≤8 years JET	After 1 hour, there was a decrease in heart rate and increase in blood pressure One patient required pacing due to bradycardia
El-Shmaa et al[99]	Prospective randomised, placebo-controlled, single centre	2010–2014	Prophylactic amiodarone versus DEX versus placebo Intravenous Amiodarone 5 mg/kg loading then 10–15 mcg/kg/hour DEX 1 mcg/kg loading then 0.5 mcg/kg/hour	90	2–18 years	Incidence of JET was reduced and shorter ICU and hospital stay in both children receiving amiodarone and DEX compared to placebo Both medications were well tolerated
Bronzetti et al[100]	Retrospective cohort, single centre	2000–2001	Flecainide Intravenous 1–2 mg/kg bolus then 0.4 mg/kg/hour	7	<30 days JET	Flecainide was effective in restoring sinus rhythm in all children Flecainide decreased heart rate and filling pressure and increased blood pressure No adverse events
Chrysostomou et al[78]	Retrospective cohort, single centre	2006–2007	DEX Intravenous 1 mcg/kg loading dose then 1 mcg/kg/hour	14	≤12 months	Arrhythmias included JET, JAR, SVT, AET DEX controlled rate/rhythm in 93% of children Adverse events included hypotension and transient AV block
Ortmann et al[101]	Retrospective cohort	2010–2014	DEX Intravenous	309	< 6 months	No difference in post-operative tachyarrhythmias in those receiving DEX and those not Increased need to treatment for arrhythmias in those not receiving DEX
Shuplock et al[102]	Prospective observational, case–control, single centre	2007–2013	DEX versus control Intravenous 0.7 mcg/kg/hour	936	<18 years	Dose-dependent risk of bradyarrhythmias with DEX No difference in tachyarrhythmias with DEX
Miyake et al[103]	Retrospective cohort, single centre	2007–2011	Landiolol Intravenous 4.7 mcg/kg/minute	10	<11 years Tachyarrhythmias after Fontan	Arrhythmias included sinus tachycardia, JET, SVT Decrease in heart rate 1 hour after start of treatment, rate control in all children No adverse events

Table 5. (*Continued*)

Saiki et al[104]	Retrospective case series, single centre		Landiolol Intravenous 1–10 mcg/kg/minute	4	<3 years	JET converted to sinus rhythm after 15 minutes No adverse events
Tokunaga et al[105]	Retrospective cohort, single centre	2006–2012	Landiolol Intravenous 11 mcg/kg/minute loading then 7 mcg/kg/minute	12	<10 years	Arrhythmias included atrial flutter, sinus tachycardia, AVRT, JET, SVT Reduction in heart rate without change in blood pressure 70% of children converted to normal sinus rhythm One patient developed bradycardia requiring pacing
Yoneyama et al[106]	Retrospective cohort, single centre	2006–2017	Landiolol Intravenous 3–5 mcg/kg/minute loading then 3–10 mcg/kg/minute infusion	10	≤5 years JET	Lower heart rate within two hours after infusion started No change in blood pressure 80% converted to sinus rhythm within 24 hours
Verma et al[107]	Prospective randomised, placebo-controlled, single centre		Magnesium versus placebo Intravenous 30 mg/kg	50	<12 months Arterial switch for TGA	Low preoperative magnesium levels that improve upon re-warming after bypass No difference in the incidence of arrhythmias

AET = atrial ectopic tachycardia; AVRT = atrioventricular reciprocating tachycardia; DEX = dexmedetomidine; ICU = intensive care unit; JAR = junctional accelerated rhythm; JET = junctional ectopic tachycardia; SVT = supraventricular tachycardia; TGA = transposition of the great arteries

Regardless of medication used, the studies included here show that younger children have more variability in how they respond to anticoagulants and highlight the need for further investigation into age-related dosing guidelines.[135–137] After single-ventricle palliation with shunt placement, 80% of neonates and infants were resistant to aspirin based on thromboelastography in the immediate post-operative period.[135] Starting warfarin early post-operatively in children with mechanical valves or Fontan circulation was associated with supratherapeutic international normalised ratio, but there were no reports of thrombotic events while waiting for warfarin to become therapeutic.[133,137] Variations in enteral absorption may contribute to variable responses in different age groups in the post-operative period, which should be further studied. For catheter-associated thrombus, heparin at low doses was safe, but did not decrease the incidence.[136] Both fresh frozen plasma and fibrinogen concentrate were effective to decrease post-operative bleeding.[134]

Steroids

Out of the 267 records retrieved by the systematic search in PubMed and EMBASE, 10 studies met the inclusion criteria and included a total of 604 children (Table 8).[139–148] All studies were single centre. There were six retrospective cohort studies and four prospective, randomised, double-blind, placebo-controlled studies. Steroids included in these studies were hydrocortisone (90%), methylprednisolone (30%), and dexamethasone (20%).

Hydrocortisone was the most common steroid given to children post-operatively, either prophylactically or for the treatment of unfavourable haemodynamics.[139,141,144,145] There were no increased rates of infection and hyperglycaemia was only seen in neonates.[146] Most children respond positively to steroids; this response was more likely in children found to have some degree of adrenal insufficiency.[141,143–145,148,149] Those who do not respond have higher mortality.[144] Longer duration of steroids is associated with lower vasopressin levels.[142] While there have been multiple prospective, randomised, double-blind, placebo-controlled trials regarding steroids, there is still a need to *a priori* define a patient population that will benefit the most from steroids.

Other endocrine medications

Out of the 162 records retrieved by the systematic search in PubMed and EMBASE, 4 studies met the inclusion criteria and included a total of 2080 children (Table 9).[150–153] Most studies were multicentre (75%), and all studies were prospective, with one being a *post hoc* analysis of a prospective, randomised controlled trial. Medications included were insulin to maintain tight glycemic control (75%) and triiodothyronine (25%).

Tight glycemic control was robustly studied in prospective, randomised, large, multicentre trials.[150–152] Although hyperglycaemia has been associated with worse outcomes and tight glycemic control is easy to achieve, it has not been shown to meaningfully improve outcomes and is associated with a higher incidence of iatrogenic hypoglycaemia.[150–152] Overall, older children had higher blood glucose and required more insulin per kg.[150–152] Other studies have shown derangements in pituitary hormones such as growth hormone and thyroid hormone after cardiopulmonary bypass.[154,155] One study evaluated the effects of triiodothyronine in children after bypass and showed an increase in contractility and cardiac index.[153] Endocrine medications have the potential to significantly alter post-operative outcomes and should be investigated further.

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Table 6. Characteristics of post-operative pulmonary vasodilator studies and study populations

Authors	Study design	Year studied	Primary intervention	n	Study population	Findings
Gothberg et al[108]	Prospective cohort, single centre		iNO Inhaled Start at 5 ppm, increase to 10 ppm, 20 ppm, 40 ppm Start at 3 ppm, increase to 10 ppm, 30 ppm, 80 ppm	12	<13 months mPAP > 20 mmHg or mPAP/mean systemic artery pressure >0.25	iNO decreased mPAP and increased PaO2 after initiation of iNO at 3 or 5 ppm Uptitration of iNO did not show further improvement No adverse events
Miller et al[109]	Prospective randomised, double-blind, placebo-controlled, single centre		iNO versus placebo Inhaled 10 ppm	124	<12 months mPAP > 25 mmHg or pulmonary pressure > half systemic pressure by echo	Lower PVRi, fewer pulmonary hypertension crises, and shorter time intubated with iNO
Morris et al[110]	Prospective randomised, cross-over, single centre		iNO or hyperventilation, then iNO and hyperventilation Inhaled 5 ppm for 15 minutes then 40 ppm Hyperventilation to pH > 7.5	12	<18 years mPAP > 25 mmHg biventricular repair	mPAP decreased with iNO and hyperventilation but PVRi had no change compared to monotherapy Hyperventilation and iNO and hyperventilation alone decreased cardiac index and increased SVRi
Tominaga et al[111]	Retrospective cohort, single centre	2010–2016	iNO during intubation versus iNO during and after intubation Inhaled 20 ppm	38	<5 years Fontan	Shorter duration of intubation and improved UOP at 6 hours, less fluid requirement, and shorter hospital stay in those receiving iNO after intubation
Wong et al[112]	Retrospective cohort, multicentre	2004–2015	iNO Inhaled	40,194	≤17 years	In those with pulmonary hypertension, iNO was associated with increased length of stay and mortality In those without pulmonary hypertension, iNO was associated with increased length of stay, no mortality difference
Journois et al[113]	Retrospective cohort, single centre	1984–1994	iNO or NMB and isoproterenol +/− prostacycline Inhaled 25 ppm	64	<35 years mPAP/systemic pressure >0.7 and decrease in arterial oxygen saturations AVCD	Reduced 30-day mortality with iNO Mortality benefit was only seen in those with severe pulmonary hypertension
Yoshimura et al[114]	Retrospective cohort, single centre	1996–2001	iNO Inhaled 5–30 ppm	47	≤16 years Fontan	CVP and TPG decreased with iNO, SVRi increased No improvement in children with CVP < 15 mmHg or TPG < 8 mmHg No iNO toxicity
Agarwal et al[115]	Retrospective cohort, single centre	2000–2003	iNO Inhaled 20–40 ppm	16	≤12 months Glenn pressures > 20 mmHg	Improvement in Glenn pressures, decreased inotropic support, improved oxygenation index at 1 and 3 hours in 79% Those who didn't respond required repeat surgery
Georgiev et al[116]	Retrospective cohort, single centre		iNO Inhaled 10–20 ppm	14	<10 years Glenn or Fontan Glenn pressures >16 mmHg or hypoxemia	iNO improved PaO2 within 1 hour, decreased Glenn pressure and TPG at 6–24 hours

Table 6. (*Continued*)

Stocker et al[117]	Prospective randomised, single centre		iNO and sildenafil Inhaled and intravenous iNO 20 ppm for 20 minutes then sildenafil 0.35 mg/kg Sildenafil 0.35 mg/kg then iNO 20 ppm	15	<12 months VSD or AVCD	mPAP decreased when iNO added first, no further decrease with sildenafil although systemic pressures decreased mPAP and systemic pressures decreased with sildenafil first, iNO further decreased mPAP but not systemic pressures Sildenafil increased oxygenation index and decreased PaO2 Cardiac index remained stable throughout
Cai et al[118]	Prospective open-label, randomised, controlled, single centre		iNO versus milrinone versus iNO and milrinone Inhaled and intravenous iNO 1–20 ppm Milrinone 0.5 mcg/kg/minute	46	<10 years TPG > 10 mmHg or CVP > 15 mmHg and hypoxemia after Fontan	Children receiving iNO and milrinone and iNO alone had lower CVP and TPG, increased systemic pressures, and improved PaO2/FiO2 At 24 hours, iNO and milrinone improved TPG and PaO2/FiO2 more than iNO alone
Loukanov et al[119]	Prospective open-label, randomised, single centre	2003–2008	iNO versus iloprost Inhaled iNO 10 ppm Iloprost 0.5 mcg/kg every 2 hour	15	<9 months mPAP > 25 mmHg with left-to-right shunt, biventricular repair	No difference in frequency of pulmonary hypertensive crises, mPAP, or duration of mechanical ventilation No adverse events
Limsuwan et al[120]	Prospective open-label, single centre	2004–2005	Iloprost Inhaled 500 ng/kg to increase to a max of 2000 ng/kg every 30 minutes up to 5 times	8	≤13 years Refractory pulmonary hypertension	Decrease in mPAP and increase in oxygen saturations 25% of children developed pulmonary congestion requiring iloprost to be discontinued
Vorhies et al[121]	Retrospective cohort, single centre	2010–2011	Iloprost Inhaled 1.25–10 mcg depending on weight every 2 hour	7	<19 months mPAP > 25 mmHg on iNO	No change in mPAP Systemic arterial blood pressure decreased after the transition to iloprost alone
Xu et al[122]	Prospective randomised, placebo-controlled, single centre	2010	Low versus high-dose iloprost versus placebo Inhaled Low-dose 30 ng/kg/minute ×10 minutes every 2h High-dose 50 ng/kg/minute ×10 minutes every 2 hour	22	<13 years >25 mmHg or mPAP > 25 mmHg or pulmonary pressure > half systemic pressure, biventricular repair	Lower mPAP/systemic blood pressure ratio compared to placebo regardless of dose 67% of those receiving iloprost had no pulmonary hypertensive crises No additional benefit from high dose, better haemodynamics with low dose
Onan et al[123]	Prospective randomised, controlled, single centre		Iloprost versus standard of care Inhaled 2 ng/kg/minute continuously	27	≤15 months mPAP > 25 mmHg, left-to-right shunt	No difference in frequency of pulmonary hypertensive crises, mPAP, duration of mechanical ventilation, ICU stay, mortality
Peiravian et al[124]	Prospective randomised, controlled, single centre	2002–2004	Sildenafil versus standard of care Enteral 0.3 mg/kg every 3 hours	42	<15 years Pulmonary artery/aortic pressure > 0.7, large septal defects	Less pulmonary hypertensive crises, shorter duration of mechanical ventilation, lower pulmonary artery/aortic pressure ratio with sildenafil No difference in length of ICU stay No significant hypotension with sildenafil

(*Continued*)

Table 6. (*Continued*)

Authors	Study design	Year studied	Primary intervention	n	Study population	Findings
Lee et al[125]	Retrospective cohort, single centre	2003–2004	Sildenafil Enteral 0.3 mg/kg every 6 hours	7	≤21 months Failure to wean iNO	Able to wean iNO after sildenafil initiation in all children No significant hypotension
Nemoto et al[126]	Prospective open-label, cohort, single centre	2003–2008	Sildenafil Enteral 0.5 mg/kg increased up to 2 mg/kg every 4–6 hours	100	<18 years old Persistent pulmonary hypertension	Decrease in mPAP after reaching goal dose of sildenafil in 82% of children TPG decreased in cavopulmonary shunts No significant hypotension
Fraisse et al[127]	Prospective double-blind, placebo-controlled, dose range, multicentre	2003–2005	Sildenafil low, medium, high dose versus placebo Intravenous 40, 120, or 360 ng/ml	17	<15 years old Pulmonary artery/Aortic pressure >0.5	Lower mPAP, shorter duration of mechanical intubation, shorter ICU stay with sildenafil Study terminated early due to slow patient accrual
Farah et al[128]	Prospective stratified and partially randomised, controlled, single centre	2008–2010	Milrinone versus sildenafil versus milrinone and sildenafil Intravenous and enteral Milrinone 0.75 mcg/kg/minute Sildenafil 0.3 mg/kg every 3 hours	48	≤12 years Pulmonary artery/Aortic pressure >0.6, left-to-right shunt	Pulmonary artery/aortic pressure ratio lower in milrinone alone group at 24 hours but significant rise in mPAP after drug discontinuation Shorter ICU stay with milrinone alone No difference in rate of hypotension
Giordano et al[129]	Retrospective cohort, single centre	2008–2012	Sildenafil versus standard of care Enteral 0.35 mg/kg every 4 hour	30	<7 years Fontan	No children had preoperative pulmonary hypertension Lower mPAP, lower inotropic requirement, shorter duration of mechanical intubation and ICU stay with sildenafil
Mendoza et al[130]	Prospective interventional study with historical comparison cohort, single centre	2000–2013	Sildenafil versus standard of care Enteral 4.6 mg/kg/day divided every 8 hours	48	<10 years Fontan	No difference in haemodynamics, duration of mechanical ventilation, ICU stay, or mortality
Schulze-Neick et al[131]	Prospective open-label, single centre		BQ123 Intravenous 0.1 mg/kg	7	<15 months Left-to-right shunt	Decrease in PVRi, mPAP, and systemic pressures with BQ123 Left atrial endothelin levels correlated to PVRi No change in cardiac index

AVCD = atrioventricular canal defect; CVP = central venous pressure; iNO = inhaled nitric oxide; mPAP = mean pulmonary artery pressure; PaO2 = arterial partial pressure of oxygen; PVRi = indexed pulmonary vascular resistance; SVRi = indexed systemic vascular resistance; TPG = transpulmonary gradient; UOP = urine output; VSD = ventricular septal defect

Table 7. Characteristics of post-operative anticoagulation studies and study populations

Authors	Study design	Year studied	Primary intervention	n	Study population	Findings
Al-Metwali et al[132]	Prospective cohort with historical controls, single centre	2015–2016	Warfarin weight-based dosing versus individualised genotype-based dosing Enteral	10	<10 years Mechanical valve placement or Fontan	Individualised dosing took longer to achieve the first therapeutic INR but less time to achieve stable anticoagulation
Lowry et al[133]	Retrospective cohort, single centre	2006–2011	Warfarin Enteral 0.2 mg/kg (0.1 mg/kg if Fontan)	59	<45 years Mechanical valve placement	Median time to reach INR ≥2 was 2 days Most variability in those < 5 years old Those on a heparin bridge took longer to reach INR of 2 No thrombotic events, significant bleeding was uncommon
Masoumi et al[134]	Prospective randomised, controlled, open-label, single centre	2014–2015	Fibrinogen concentrate versus FFP Intravenous Fibrinogen concentrate 70 mg/kg FFP 10 ml/kg	90	<24 months Fibrinogen <200 mg/dl and bleeding	Fibrinogen and FFP reduced chest tube output Fibrinogen lead to higher plasma fibrinogen levels at 24 hours
Mir et al[135]	Prospective observational, single centre		Aspirin Enteral 20 mg	20	≤75 days Single ventricle	80% of children were aspirin resistant using TEG Aspirin may not be adequate for shunt prophylaxis in the immediate post-operative period
Schroeder et al[136]	Prospective randomised, double-blind, placebo-controlled, single centre		Heparin or placebo Intravenous 10 U/kg/hour	90	<1 year	Heparin infusion did not reduce catheter-related thrombus but was safe More pronounced increase in PTT in neonates
Thomas et al[137]	Retrospective cohort, single centre	2009–2012	Warfarin Enteral 0.07 mg/kg	32	<5 years Fontan	Supratherapeutic INR occurred in 12.5% of children Supratherapeutic INR occurred more often in children starting warfarin earlier No thromboembolic events Clinically significant bleeding associated with supratherapeutic INR
Vorisek et al[138]	Retrospective cohort, single centre	2016–2017	Heparin Intravenous Low dose < 15 U/kg/hour High dose ≥15 U/kg/hour	996	<18 years	Higher risk of bleeding and thrombus with high-dose heparin than low dose or no anticoagulation

FFP = fresh frozen plasma; INR = international normalized ratio; PTT = partial thromboplastin time; TEG = thromboelastography

Table 8. Characteristics of post-operative steroid studies and study populations

Authors	Study design	Year studied	Primary intervention	n	Study population	Findings
Ando et al[139]	Prospective double-blind, randomised, controlled, single centre	2002–2004	HC versus placebo Intravenous 0.18 mg/kg/hour for 3 days, 0.09 mg/kg/hour for 2 days, 0.045 mg/kg/hour for 1 day	20	<28 days Biventricular repair	Higher cortisol levels, improved LV shortening fraction, lactate, and 3-day fluid balance with HC No increased infection rate
Dilal et al[140]	Prospective blinded, randomised, single centre		Methylprednisolone versus no drug Intravenous 30 mg/kg	100	≤15 years Tetralogy of Fallot	Increased hyperglycaemia with methylprednisolone No difference in length of stay or mechanical ventilation duration No increased rate of infection
Maeda et al[141]	Retrospective cohort, single centre	2004	HC in infants with and without adrenal insufficiency Intravenous 4 mg/kg/day divided every 6 hours for 2 days then 2 mg/kg/day divided every 6 hours for 2 days then 1 mg/kg/day divided every 6 hours × for 2 days	32	<3 months	22% of infants had adrenal insufficiency HC increased MAP and urine output in those with adrenal insufficiency only
Mastropietro et al[142]	Retrospective cohort, single centre	2008–2009	HC, dexamethasone, methylprednisolone versus no steroids Intravenous HC 1.5 mg/kg every 6 hours Dexamethasone 0.5 mg/kg every 6 hours Methylprednisolone 10 mg/kg every 12 hours	69	<18 years HC for haemodynamic compromise, dexamethasone periextubation, methylprednisolone post-transplant	Half received some steroids in the first 48 hours' post-op Increased duration of steroid therapy associated with lower AVP levels
Millar et al[143]	Retrospective cohort, single centre	2001–2003	HC, dexamethasone, methylprednisolone Intravenous 4 mg/kg/day of HC equivalents	51	<12 years Glucocorticoids for hypotension	Less inotrope and fluid requirement, increased MAP and urine output with steroids 44% of children responded with improved haemodynamics No gastrointestinal bleeding or hyperglycaemia
Neunhoeffer et al[144]	Retrospective cohort, single centre	2000–2010	HC Intravenous 100 mg/m^2/day	166	<17 years Refractory hypotension	All children >1 year responded to hydrocortisone with increased MAP, urine output, decreased lactate, and inotropic support 82% of children <1 responded Non-responders had higher mortality No hyperglycaemia
Robert et al[145]	Prospective randomised, double-blind, placebo-controlled, single centre	2012–2013	HC versus placebo Intravenous 50 mg/m^2 then 50 mg/m^2/day infusion	40	<28 days	Decreased LCOS, shorter time with inotropic support, improved urine output and fluid balance with HC No difference in duration of mechanical ventilation or ICU stay 24% of placebo group required steroid rescue for refractory hypotension No adverse events

Table 8. (*Continued*)

Suominen et al[146]	Prospective randomised, double-blind, placebo-controlled, single centre	2012–2014	HC versus placebo Intravenous 0.2 mg/kg/hour for 2 days then 0.1 mg/kg/hour for 2 days then 0.05 mg/kg/hour for 1 day	40	<28 days	Lower inotrope requirements and earlier sternal closure with steroids No difference in length of stay or mechanical ventilation duration Increased hyperglycaemia with steroids
Teagarden and Mastropietro[147]	Retrospective cohort, single centre	2011–2013	HC Intravenous 1 mg/kg every 6 hours	24	<21 HC for haemodynamic instability	58% had a positive response to HC Those that responded had lower cortisol levels prior to HC
Verweij et al[148]	Retrospective cohort, single centre	2005–2008	HC Intravenous 45 mg/m^2 × 4 if cortisol <100 nmol/L 48 mg/m^2 × 4 if cortisol >100 nmol/L	62	<7 years HC for resistant LCOS	Increased MAP and urine output, decreased inotrope requirement and lactate with HC No difference between low or normal cortisol

AVP = arginine vasopressin; HC = hydrocortisone; ICU = intensive care unit; LCOS = low cardiac output syndrome; LV = left ventricular; MAP = mean arterial pressure

Table 9. Characteristics of other post-operative endocrine studies and study populations

Authors	Study design	Year studied	Primary intervention	n	Study population	Findings
Agus et al[150]	Prospective randomised, two centres	2006–2012	Tight glycemic control (BG 80–100 mg/dl) versus standard of care	980	≤36 months	No change in rate of infections, mortality, length of stay, organ failure Glucose control is easily achieved with low rates of hypoglycaemia
Agus et al[151]	*Post hoc* analysis of a prospective randomised, two centres	2006–2012	Tight glycemic control (BG 80–100 mg/dl) versus standard of care	980	≤36 months	Tight glycemic control may lower risk of infection in children >60 days old
Kanthimathinathan et al[152]	Prospective randomised, controlled, mutlicentre	2008–2011	Tight glycemic control (BG 72–126 mg/dl) versus standard of care	80	<16 years	Older children had higher BG and required more insulin per kg
Bettendorf et al[153]	Prospective randomised, double-blind, placebo-controlled, single centre	1994–1995	Triiodothyronine versus placebo Intravenous 2 mcg/kg on day 1, then 1 mcg/kg daily	40	<11 years Receiving post-operative dopamine	Plasma triiodothyronine levels were low after bypass Cardiac index increased more in the treatment group No delay in thyroid function recovery No adverse events

BG = blood glucose

Discussion

Current knowledge gaps

We identified 127 studies in 51,573 children across all medication classes. Overall, most studies were small, single-centre cohorts without standardised endpoints. A lack of standardised endpoints makes comparisons between studies difficult. For example, inotropic study endpoints included various combinations of central venous pressure, urine output, lactate levels, mean arterial pressure, partial pressure of arterial oxygen, oxygenation index, cardiac index, and LCOS. Which endpoints translate to meaningful clinical outcomes are unknown, and acceptable endpoint values may vary by age and disease state.[156]

In all medication classes, drug dose and interval varied widely, in part due to lack of label or other consensus-based recommendations. This complicates the evaluation of dose–efficacy and dose–safety relationships in this population.[157] For example, with diuretics, there is a lack of consensus of starting low or high dose, or as continuous versus intermittent intravenous dosing. Because fluid overload has been associated with increased mortality, optimal dosing may have a significant impact on outcomes.[158]

In an attempt to overcome limited enrolment, many studies include patients of different ages and with varying cardiac lesions. 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. While studies of frequently used medications, such as vasoactives, may enrol sufficient numbers to identify age- and disease-related differences, other less commonly used drugs, such as antiarrhythmics or pulmonary vasodilators, require innovative approaches. These may include studies that use available RWD, such as dosing and demographic information from the electronic health record, combined with standardised master protocols and advanced PK/PD modeling to inform drug dose–exposure–response relationships. These studies may identify age- and disease-related factors that affect drug disposition, and decrease the number of patients needed for prospective validation, safety, and efficacy trials.[159,160]

Limitations

Our study is not without limitations. In order to broadly classify post-operative medication management, our inclusion criteria were narrow. Studies investigating medications in all critically ill children (not just those with CHD undergoing repair or palliation with cardiopulmonary bypass) were excluded. Trials in children without CHD may offer important insight into the impact the disease has on drug disposition and should be explored further. Additionally, we only included studies published from 2000 to 2019. This potentially biases our search towards newer medications, as evidenced by few studies of epinephrine or dopamine, two of the more commonly used vasoactive medications. However, it is important to compare newer medications with older, "standard of care" drugs, to continue to investigate how older drugs are affected by development and disease process, and to ensure safety and efficacy of these drugs in the context of modern perioperative management. Therefore, we hope that the years included in our systematic literature review have appropriately captured studies that are reflective of our patient population in the context of current practice.

Future directions

To close existing knowledge gaps in post-operative pharmacotherapy, novel approaches that facilitate enrolment in meaningful clinical trials or alternative evidence generation methods are needed. One major limitation in the current body of evidence is the inability to definitively conclude the efficacy or safety of medications due to inconsistent, non-validated endpoints and variable inclusion and exclusion criteria.

Hard clinical endpoints, such as cardiac output or mortality, are difficult to measure or require large sample sizes to identify a treatment effect. In paediatric trials, surrogate or composite endpoints are an attractive alternative,[14] but are not always validated. With the increase in the collection of haemodynamic data post-operatively and availability of biomarkers, surrogate endpoints are more readily available. Studies validating these data as surrogate endpoints are needed so that feasible, clinically meaningful endpoints can be included in trial design.[9] Consistent inclusion and exclusion criteria that are broad enough to account for age- and disease-related effects on drug disposition, but narrow enough to not obscure efficacy or safety signals should also be defined.[161]

The infrastructure and flexibility of master protocols combined with RWD collection may be one way to remedy the current challenges of post-operative pharmacotherapy trials. Master protocols consist of a standardised trial network infrastructure, and the use of a common protocol.[162] While this requires upfront planning and resources, it allows for a long-term standardised protocol structure that is easily translatable to multiple diseases or medications. This could be implemented alongside current collaborations, such as the Pediatric Cardiac Critical Care Consortium (PC4) and the Pediatric Acute Care Cardiology Collaborative (PAC3), whose data collection platforms and site penetration may provide the numbers needed to study relatively rare disease processes while minimising duplicate data collection efforts. These valuable collaborations have already highlighted the variation in care across centres and even suggest that collaboration and transparency play a role in improving outcomes.[163,164] Additionally, the post-operative setting generates innumerable RWD points including laboratory values and haemodynamic parameters that, when collected in an accessible manner, can provide valuable evidence for clinical trials. A master protocol geared towards the post-operative setting could easily be tailored to drug-, disease-, or age-specific parameters and use the data already collected post-operatively to inform clinical practice. Drug development efforts using novel trial design should focus on this complex, heterogeneous population so that drugs can be used efficaciously and safely in the high-risk post-operative period.

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