Evaluating the Efficacy of Calcium Chloride versus Calcium Gluconate in ECMO Initiation for Neonates

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Abstract

Purpose: Neonates who require Extracorporeal Membrane Oxygenation (ECMO) are at risk for calcium derangements and associated adverse outcomes. A large children's hospital in the Southwest changed their practice from using calcium gluconate in priming their neonatal ECMO to using calcium chloride. The impact of this change was not investigated.

Methods: A retrospective chart review of 56 neonates who required ECMO support one year prior to and one year following the practice change was conducted. Descriptive data was collected along with the first ionized calcium measured following ECMO initiation.

Results: Upon review of the data, the post-ECMO calcium levels were not significant between the calcium gluconate and calcium chloride groups using a Mann Whitney U test ($U = 315.5$, $z = -1.25$, $p = .213$). However, a Chi-square test was significant ($\chi^2(1) = 4.94$, $p = .026$) for having calcium values outside of a normal range in the calcium gluconate group. Fisher's exact test revealed an odds ratio of 3.43 for the first calcium being outside normal range in the calcium gluconate group.

Implications: While comparison of the first measured ionized calcium post-ECMO between the two groups was not statistically significant, there was a significant correlation with normal post-ECMO calcium in the calcium chloride group. This suggest that both calcium gluconate and calcium chloride are appropriate for use in priming the neonatal ECMO circuit, however calcium chloride may provide tighter control of calcium during ECMO initiation in neonates.

Keywords: ECMO, Neonate, Calcium

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Extracorporeal Membrane Oxygenation (ECMO) is a lifesaving medical modality. ECMO uses mechanical devices to provide support of the lungs and the heart in states of severe illness. This mechanical support allows the organs to rest and recover. Centers that provide ECMO have similar policies and procedures. Each institution strives to improve upon their practice and deliver better patient outcomes.

Problem Statement

The Extracorporeal Life Support Organization (ELSO) is an international consortium that supports the development and evaluation of therapies that support failing organ systems (ELSO, 2020). The ELSO (2017) publishes general guidelines, which outline ECMO recommendations. Regarding the priming of the ECMO circuit, the ELSO (2017) recommends the addition of calcium. The type of calcium, whether calcium gluconate or calcium chloride, is not specified in the guidelines.

Purpose and Rationale

Neonates placed on ECMO have exposure to a large volume of blood products in a short time. Whole blood and packed red blood cells are stored with acid citrate dextrose or citrate phosphate dextrose to prevent coagulation (Ogunlesi et al., 2017). These agents cause a chelating effect on serum calcium, which can lead to severe hypocalcemia (Giancarelli et al., 2015). The volume of blood required to prime the ECMO circuit approaches or even exceeds the circulating volume of a neonate (Fikac, 2019). This exposure led ELSO to recommend that when priming the ECMO circuit with blood, calcium should be added, though they do not specify what form of calcium.

A large children's hospital in the southwest that offers ECMO support to neonatal patients had been using calcium gluconate in the prime of the ECMO circuit. They then changed their practice to using calcium chloride. The purpose of this paper is to evaluate the impact of this practice change.

Background and Significance

ECMO in the Neonatal Population

Bhatt et al. (2018) found that between 2002 and 2011, 7,603 neonatal patients were placed on ECMO in the United States. These patients were at high risk for mortality without ECMO support. Bhatt et al. (2018) also found a downtrend in mortality for neonates on ECMO from 2002 to 2011, indicating an improvement in outcomes for these patients. Mortality for patients born with congenital heart defects is reduced with the use of ECMO, which allows for recovery following prolonged and complex surgical repairs (Roeleveld & Mendonca, 2019). ECMO is the critical therapy that allows for the survival of neonates with diagnoses such as diaphragmatic hernia, hypoxic-ischemic encephalopathy, sepsis, and congenital heart defects. Neonatal patients present increased complexity for ECMO from the fluid shifts caused by the proportionally large priming volumes for going onto ECMO; the lower blood flow through the circuit increasing the likelihood of thrombus formation; and the small size of the cannulas used to place the patients on ECMO (Roeleveld & Mendonca, 2019). Church et al. (2016) proposed that survival and complication rates for ECMO may even be acceptable for neonates of 29-weeks gestation age and above.

Effect of Blood Products on Calcium

The importance of calcium during the administration of large volumes of blood products is seen in adults requiring massive transfusions for trauma. Giancarelli et al. (2015) found that

hypocalcemia is common in patients requiring massive blood product transfusion, resulting in higher mortality for those that developed sever hypocalcemia. The authors note that in states of poor perfusion, as with massive transfusion, the patient's ability to clear citrate hepatically is impaired, increasing the likelihood of hypocalcemia (Giancarelli et al., 2015). Moore et al. (2020) also found that in patients with prehospital plasma administration, patients experienced significantly higher rates of hypocalcemia, and severe hypocalcemia was associated with decreased survival.

Infants with high bilirubin at birth may undergo an exchange blood transfusion (EBT) where most of the neonate's circulating blood is carefully replaced. This transfusion involves the administration of a proportionally large volume of blood products to the neonate. Ogunlesi et al. (2017) found that evidence suggests prophylactic administration of intravenous calcium reduces hypocalcemia in neonates who receive EBT.

Calcium Gluconate versus Calcium Chloride

Turner et al. (2016) identify hypocalcemia as a medical emergency, and recommend the use of calcium gluconate for replacement in the adult population with ECG monitoring in light of the fact that calcium chloride is an irritant and should only be administered via central venous access. Calcium gluconate has 4.6 mEq/gm, while calcium chloride has 13.6 mEq/gm (Ruppel, 2012). Calcium gluconate has less risk of extravasation injury and is favored for intravenous administration. However, when using calcium in the priming of an ECMO circuit, there is no risk of extravasation for the patient.

Internal Evidence

A large free-standing children's hospital in the Southwest commonly uses ECMO to support critically ill patients. The ECMO team at this institution had been using calcium

gluconate in the prime of ECMO circuits for neonatal patients, and calcium chloride in the ECMO circuit prime for older patients. The practice was then changed to standardize the use of calcium chloride to prime the ECMO circuit for all patients placed on ECMO. The impact of this practice change has not been evaluated, and has led to the PICO question: "In the neonatal ECMO population, does the use of calcium chloride in the ECMO circuit prime improve serum calcium levels when compared with the use of calcium gluconate in the ECMO circuit prime?"

Search Strategy

Sources and Process

Three databases were searched to review evidence to answer the PICOT question: PubMed, CINAHL, and Cochrane. These databases were selected because they encompass high-quality medical literature relevant to the PICOT question. All three databases yielded relevant material.

Inclusion Criteria and Keywords

To capture research relevant to all aspects of the PICOT question, various keywords and combinations of keywords were employed. Keywords relevant to the population included *neonate, ECMO, and the combination of neonate and ECMO.* To capture the complexity of the intervention and control for the PICOT question, the keywords *calcium, blood transfusion, exchange blood transfusion,* and the combinations of *hypocalcemia and ECMO, calcium and ECMO, hypocalcemia and neonate, exchange blood transfusion and neonate,* and *calcium and blood transfusion* were used. Publication dates for all searches were limited to the last five years. All searches were limited to peer-reviewed publications. Studies were excluded if they were not in English.

Search Yield

The combination of searches with the key terms on CINAHL yielded 728 articles in total. Articles were appraised for relevance to the population and topic. Searches in PubMed yielded 251 articles, which were appraised for relevance to the topic. Cochrane yielded 56 trials that were appraised for relevance. One Cochrane Review was found pertinent to the topic as well. The searches covered a broad range of clinical topics, so articles were more closely examined for type of study performed, and proximity to the PICOT population and intervention. Ten articles were chosen for review based on relevance to the research question and quality of evidence.

Critical Appraisal and Synthesis of Evidence

Of the ten articles selected for review, one weak meta-review was found that included one qualifying study. Seven of the studies selected were retrospective cohorts with widely varying sample sizes and populations. Two studies were meta-synthesis of current evidence related to neonatal ECMO. Three studies were done in adult populations, while seven studies were from the neonatal or pediatric population. Four studies involved the administration of large amounts of blood products. Six of the studies looked at patient calcium levels. Giancarelli et al. (2016) specifically suggested the use of calcium chloride with massive transfusion in adults, however, this was not a part of the study design. No study looked at the use of calcium chloride versus calcium gluconate. The patient population in adult studies related to massive transfusion were heterogenous with a wide range in patient ages. Studies on massive transfusion looked at a homogenous diagnosis of trauma. Studies involving neonatal ECMO were fairly homogenous regarding patient age and diagnosis.

The Evaluation Table (Appendix A, Table A2) shows that the studies looking at calcium derangements in massive transfusion found strong correlations with negative patient outcomes. The study by Ho and Yip (2016) supports the role of calcium in clotting for critically ill patients.

There was limited evidence that looked specifically at calcium in neonates on ECMO. The study by Kaplan and Heath (2019) identified increased risk factors for calcium derangements for neonates on ECMO, and some of the negative outcomes that were associated with abnormal calcium levels for these patients. Four studies found other factors that placed patients at higher risk for mortality.

Conclusions and Discussion

Synthesis of the evidence reviewed suggests calcium derangements are correlated to poor outcomes in critically ill patients. Calcium derangements are consistently associated with large volumes of blood product administration and ECMO. One study by Kaplan and Heath (2019) found that abnormal calcium levels in neonatal or pediatric patients on ECMO were associated with longer ECMO duration, increased ICU and hospital length of stay, and acute kidney injury. None of the evidence reviewed discussed the use of calcium chloride versus calcium gluconate, highlighting a gap in current evidence on this topic.

The use of calcium in the priming of the ECMO circuit is a unique form of calcium administration. The evidence describing calcium administration during massive transfusion did not discuss factors influencing the choice between calcium chloride or calcium gluconate. Often, calcium gluconate is used when a patient only has peripheral intravenous access. For neonates who require ECMO, choosing the type of calcium based on the type of intravenous access is not relevant, as the calcium is not administered directly to the patient. The PICOT question driving this inquiry may yield new insight into the best practice for calcium administration for neonates who require ECMO.

Theory Application

The role of calcium in reducing negative outcomes for neonates in ECMO is rooted in the physiologic model of the role that calcium plays in homeostasis. Calcium is the most abundant ion in neonatal circulation and is important for nerve conduction, bone formation, muscle contractility, and coagulation (Perino, 2020). Calcium is also needed for platelet adhesion, stabilizing fibrinogen, and clotting factors II, VII, IX, and X (Giancarelli et al., 2015). Derangements of this electrolyte for the neonate can lead to apnea, seizures, arrhythmias, and poor vascular tone (Perino, 2020). Neonates who require ECMO may experience severe calcium disturbances, and potential long-term damage to calcium regulation (Rambaud et al., 2015).

Implementation Framework

The Define, Measure, Analyze, Improve, Control (DMAIC) model for quality improvement provides a framework for careful analysis of quality measures. The linear approach outlined by DMAIC is shown in Appendix B. The steps of this process include defining the opportunity for improvement and project goals, identifying and developing measurement systems, analyzing input, determining areas of improvement, and controlling outcomes by making process changes if needed (Berardinelli, 2012).

The management of a neonate on ECMO is inherently complex. The physiologic role of calcium in the body underpins the need to ensure maintenance of normal calcium levels for neonates who require ECMO. Taking a systematic approach to examine a practice change impacting calcium levels helps identify what specific factors among many influence the process as a whole. The goal of DMAIC is to improve efficiency, improve outcomes, and reduce errors (Berardinelli, 2012). This method requires careful examination of many components that will influence the final outcome.

Methods

A single center, retrospective chart review was conducted for patients under 15 kilograms who required ECMO one year prior to and one year following the practice change. This center offers ECMO throughout care areas and had between 37 and 46 ECMO cannulations in the three years when data was collected. The project was approved by the Institutional Review Board as exempt. Patients cannulated for ECMO were located in the neonatal, cardiovascular, and pediatric intensive care units and the operating room. Patients over 15 kg were excluded as the institution used the cutoff weight of 15 kg to determine who received calcium gluconate prior to the practice change. Patients with more than one course of ECMO within the date rage were included, with each distinct cannulation recorded. Twenty-seven cannulations were identified for the calcium gluconate group and 29 for the calcium chloride group.

Descriptive data collected included: patient weight, neonatal or pediatric categorization used by the ECMO team, age in days, date and time of ECMO initiation, date and time of ECMO decannulation, number of ECMO patient days, categorical indication for ECMO, type of ECMO cannulation, ECMO outcome, hospital length of stay, initiation of extracorporeal cardiopulmonary resuscitation (ECPR), and use of continuous renal replacement therapy (CRRT). Laboratory values collected included pre and post ECMO ionized calcium if available, blood pH from either arterial or venous blood gas sampling, blood lactate from arterial or venous blood gas, and platelets. Laboratory values closest to the time of cannulation were recorded.

The primary inquiry of this project was the effect on patient calcium levels immediately following ECMO cannulation in each group. To identify patients with ionized calcium values outside of the institution’s reference range of 4.6 to 5.17 mg/dL, each ionized calcium value was categorized as inside reference range (I) or outside reference range (O).

Descriptive statistics were evaluated to summarize each group. Shapiro-Wilk tests were used to determine if the distributions of pre and post ECMO ionized calcium were normal. A two-tailed, Mann-Whitney two-sample rank-sum test was evaluated for post-ECMO ionized calcium values to compare the two groups. A Fisher's exact test was used to determine the relationship of each calcium group and ionized calcium values inside or outside of the reference range.

Results

For both groups, the most frequent categorical indication for ECMO was cardiac (n = 20, 74% vs. n = 13, 45%). The ECMO outcome was similar in both groups, with survival to discharge n = 11 in the calcium gluconate group and n = 15 in the calcium chloride group. The number of patients requiring ECPR initiation, CRRT use, and mode of ECMO were also similar. Frequencies and percentages are presented in Appendix C, Table 1.

The average weight in the calcium gluconate group was 6.11 kg (SD = 2.44, SE_M = 0.47, Min = 3.00, Max = 10.40, Skewness = 0.48, Kurtosis = -1.08), and for calcium chloride, 5.55 kg (SD = 2.22, SE_M = 0.41, Min = 2.15, Max = 10.47, Skewness = 0.64, Kurtosis = -0.63). The calcium gluconate group had an average of 7.11 ECMO patient days and 111.96 days hospital length of stay. The calcium chloride group's average for ECMO patient days was 8.52, with an average of 77.41 days hospital length of stay. Patient age at initiation was similar for both groups (176.93 vs. 155.52). The summary statistics can be found in Appendix C, Table 2.

Shapiro-Wilk tests revealed post-ECMO ionized calcium had distribution significantly different from normality based on an alpha of 0.05 (W = 0.86, p < .001).Since post-ECMO ionized calcium was not normally distributed, a non-parametric Mann-Whitney U test was

chosen to compare the calcium chloride and calcium gluconate groups. The result of the two-tailed Mann-Whitney *U* test was not significant based on an alpha value of 0.05, $U = 315.5$, $z = -1.25$, $p = .213$. Table 3 in Appendix C presents the result of the two-tailed Mann-Whitney *U* test. Figure 1 in Appendix C presents a boxplot of the post-ECMO ionized calcium values between the two groups.

The results of the Fisher exact test were significant based on an alpha value of 0.05, $p = .033$, suggesting that the calcium group and post-ECMO ionized calcium are related to one another. Since the Fisher's exact test was conducted for a 2x2 contingency table, with an odds ratio of 3.43, indicating that the odds of observing calcium gluconate and post-ECMO ionized calcium outside reference range is 3.43 times as likely as observing calcium chloride and an ionized calcium outside range. The results of the Fisher's exact test are presented in Appendix C, Table 4.

Discussion

The data analysis confirms that there was no significant difference in the first measured ionized calcium following ECMO cannulation between the calcium gluconate and calcium chloride group. This was demonstrated by the Mann-Whitney *U* ($p = .213$). This project did find a significant relationship in the calcium gluconate group and the first measured calcium being outside the reference range. Correspondingly, the calcium chloride group had more post-ECMO ionized calcium values inside the reference range (n = 20) compared to the calcium chloride group (n = 13).

Clinically, maintaining normal calcium when a neonate is placed on ECMO regulates an already tenuous situation. The role of calcium in maintaining adequate vascular tone, hemodynamic stability, and preventing coagulation derangements heightens its importance

during ECMO cannulation. The findings of this project suggest that while both calcium chloride and calcium gluconate may be acceptable for use in the ECMO prime, calcium chloride may provide tighter control in this critical situation.

There were some important limitations to this project. Firstly, the sample was only powered to detect a large effect size. To be able to detect a small effect size, a sample of 834 cannulations or more would have been required (Buchner et al., 1997). However, no single ECMO center has near that volume of neonatal cannulations. A retrospective analysis across centers potentially could yield a large enough sample, but also would be challenging. The ECMO prime varies from one center to the next in numerous ways making it difficult to isolate the effect of the form of calcium used. Another important limitation of this project was the small window of time that patient calcium levels were evaluated. The effect of the ECMO prime on patients is mitigated by ongoing interventions to correct imbalances and derangements in the hours and days following cannulation. Th calcium chloride and calcium gluconate groups were similar in outcomes including ECMO duration, length of stay, and survival.

Implications for Practice Change and Potential Outcomes

Given the lack of recent evidence regarding the use of calcium gluconate versus calcium chloride for neonates on ECMO, there is not an explicit precedent to follow. This project suggests that while both forms are acceptable, calcium chloride provides better control of patient calcium with ECMO initiation. While further investigation is warranted, this project identified calcium chloride as the best practice for priming the neonatal ECMO circuit and may inform the current variation in practice between ECMO centers.

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Appendix A

Evaluation and Synthesis Tables

Table A1

Evaluation Table

Citation	Theory/Conceptual Framework	Design/ Method	Sample/ Setting	Major Variables & Definitions	Measurement/ Instrumentation	Data Analysis	Findings/ Results	Level/Quality of Evidence; Decision for practice/ application
Giancarelli et al. (2016). Hypocalcemia in trauma patients receiving massive transfusion. No disclosures, funding not mentioned: US	Not stated, implied physiologic role of calcium with citrated blood administration	Retrospective: determine incidence of hypocalcemia/ severe hypocalcemia in MT	n = 156 trauma Pts > 18 yrs who had activation of MT, single Level 1 Trauma Center	IV- MT for trauma DV- hypocalcemia	Hypocalcemia = iCa <1.12mmol/L Severe hypocalcemia iCa < 0.90mmol/L	Chi-square, Mann-Whitney U, two tailed tests for significance	Overall incidence hypocalcemia 97.4% (n=152), incidence severe hypocalcemia 71% (n=111); mortality higher in severe hypocalcemia (49% vs. 24%); Severe hypocalcemia got more blood products (34 vs 22); significant hypocalcemia associated with increased aPTT, increased lactate, lower plts, and lower pH	Level III- retrospective cohort Strong evidence of hypocalcemia with MT. Good sample size, may variables examined. Authors state that their data may support the use of Ca chloride. Supports administration Ca with MT, and association of hypocalcemia with poor outcomes.
Ogunlesi et al. (2017). Prophylactic intravenous calcium therapy for exchange blood transfusion in the newborn. No conflict of	Not stated, implied physiologic model of the role of calcium with citrated blood administration	Cochrane review- meta analysis to determine if prophylactic Ca reduced hypocalcemia-related morbidities	N-1 (study included 30 participants with infants who had EBT at single center, term neonates, no blinding)	IV- administration Ca gluconate 1Ml/100mL of blood DV- mortality, mean serum Ca, mean iCa	Meta-analysis not completed due to only one study identified, GRADE approach for quality of evidence	Statistics that would have been used for Meta-analysis were described but not used	No difference in mortality, total mean serum Ca raised MD -0.46, and mean serum iCa raised MD -0.22 in intervention group, 1 death per group	Unable to complete level I meta-review Level II case controlled trial, authors describe as "poorly executed" and not enough evidence to support prophylactic Ca in

Key: **AKI** – Acute kidney injury; **aPTT**- activated partial thromboplastin time; **Ca** – Calcium; **iCa**- Ionized Calcium; **DV**-dependent variable; **ECMO** – Extracorporeal Membrane Oxygenation; **EBT**- Exchange Blood Transfusion; **ICU** – Intensive Care Unit; **IV**- independent variable; **LOS** – Length of Stay; **MA** – maximum amplitude; **MD** – mean deviation; **Mg**- Magnesium; **MT** -Massive Transfusion; **N**-number of studies; **n**- number of participants; **Phos-** Phosphorus; **PICU** – Pediatric Intensive Care Unit; **Plts**- platelets; **Pt** – Patient; **PTH** – Parathyroid hormone; **TEG** – thromboelastograph; **VA** – venoarterial; **VV** – venovenous; **yrs**- years

Citation	Theory/Conceptual Framework	Design/ Method	Sample/ Setting	Major Variables & Definitions	Measurement/ Instrumentation	Data Analysis	Findings/ Results	Level/Quality of Evidence; Decision for practice/ application
interest. Funding not mentioned: Nigeria		and death among newborns receiving EBT				as only one study qualified for inclusion		EBT. Weak support of Ca administration with EBT
Rambaud, et al. (2015). Calcium homeostasis disorder during and after neonatal extracorporeal membrane oxygenation. No financial support or conflicts: France.	Not stated, implied physiologic model of neonatal calcium dysregulation after ECMO	Retrospective cohort study to confirm Ca homeostasis dysregulation in neonates under ECMO	n= 11 neonates on ECMO in single center PICU; 37-42 weeks; 1-15 days old; lactate 1.7-11	IV- Neonates on ECMO DV- PTH, serum Mg, Ca, iCal, Phos, PTH, urinary Ca, urinary Phos	Serum Ca, iCa, Phos, Mg, PTH, urinary Ca, urinary Phos	Pearson's test $p<0.05$	All Pts had moderate hypercalcemia 6 months after ECMO weaning; no correlation of PTH with MG	Level III- retrospective cohort. Highlights presence of Ca derangement in neonates with ECMO, study not focused on Ca administration with ECMO initiation, small sample size
Ho et al. (2016). Concentration-dependent effect of hypocalcaemia on in vitro clot strength in patients at risk of bleeding: A retrospective cohort study. Funded by Department of Intensive Care, Royal Perth Hospital: Australia	Not stated, implied Physiologic model: Ca is related to clot strength *in vitro*	Retrospective study of Pts with risk for bleeding	n = 610 Pts at risk for bleeding or with active bleeding in ICU at single center	IV- iCa DV- MA on TEG	iCal, TEG for MA	Pearson correlation coefficient and multiple linear regression	iCa had concentration-dependent association with *in vitro* clot strength after adjusting for other coagulation abnormalities; iCa correlation with MA; with low Plts iCa had greater influence on clot strength	Level III retrospective cohort study Maintaining normal iCa during critical bleeding recommended; large sample size, critically ill adult population with more derangements in MA with illness
Kaplan et al. (2019). Evaluation of calcium homeostasis and dietary supplementation for pediatric and	Not stated, implied physiologic model of calcium derangement with ECMO	Single center retrospective cohort review Ca and ECMO	n=78 neonate/pediatric Pts on ECMO >48hours; 36 neonates, 42 pediatric; 88% VA, 8% VV; 1	IV= iCa DV= ECMO duration, AKI, survival to decannulation, survival to discharge,	iCa, chart review ECMO duration, survival to decannulation, survival to discharge, ICU	Pearson Chi-square, Mann-Whitney U-test for comparison	Abnormal Ca group younger, weight less, had sigher creatinine; abnormal Ca associated with longer ECMO,	Level III retrospective cohort Recommend minimizing disturbances in Ca when on ECMO to improve outcomes;

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Citation	Theory/Conceptual Framework	Design/ Method	Sample/ Setting	Major Variables & Definitions	Measurement/ Instrumentation	Data Analysis	Findings/ Results	Level/Quality of Evidence; Decision for practice/ application
neonatal patients receiving extracorporeal membrane oxygenation support. No conflict of interest of private funding: US			Pt transitioned from VA to VV	length of stay in ICU, hospital LOS	LOS, hospital LOS	groups odds ratio for AKI	greater hospital & ICU LOS, increased AKI; 65% had 1 abnormal iCa, 35% no abnormal iCa, 43% had both high and low iCa	moderate sample size, diverse pediatric population; large VA sample size which is unusual; Ca derangements associated with undesired outcomes and increased LOS
Church et al. (2017). Pushing the boundaries of ECLS: Outcomes in <34 week EGA neonates. No private funding, no conflict of interest: US	Not stated, implied challenge to accepted neonatal ECMO gestational age	Retrospective study from ELSO registry	n=752 29-34 week neonates between 1976-2008 on ECMO (n= 243 29-33 wk; n= 509 34 wk)	IV- gestational age DV- ECMO survival	Birthweight, gestational age, survival, pre-ECMO conditions, complications	t-test, Chi-square, logistic regression	Survival statistically different for 29-33 week, increase cerebral infarct in 29-33 week group, survival not correlated with gestational age	Level III retrospective cohort; Modest difference in survival and cerebral infarction may be clinically acceptable and authors suggest <34 week not absolute contradiction to ECMO
Schueller et al. (2017). In-hospital outcomes following extracorporeal membrane oxygenation in a retrospective cohort of infants. No funding or conflict of interest: US	Not stated; examination of potential physiologic factors that influence neonatal ECMO survival	Retrospective cohort from single center from 1998 to 2013	n=268 infants >32 weeks and >1,800g on ECMO; 17% premature	IV= postnatal age, AKI, cannulation type DV= ECMO survival	Gestational age, cannulation type, AKI by creatinine,	Chi-square, fisher's exact, and Wilcoxon rank sum, logical regression	Cannulation type, postnatal age, ECMO duration 7-13 days, and AKI were associated with lower ECMO survival, prematurity was not; 87% survival to discharge, 92% survival to decannulation	Level III retrospective cohort Identified risk factors for decreased ECMO survival; prematurity alone may not decrease survival; providers should consider comorbidities and timing of ECMO to improve outcomes

Key: **AKI** – Acute kidney injury; **aPTT**- activated partial thromboplastin time; **Ca** – Calcium; **iCa**- Ionized Calcium; **DV**-dependent variable; **ECMO** – Extracorporeal Membrane Oxygenation; **EBT**- Exchange Blood Transfusion; **ICU** – Intensive Care Unit; **IV**- independent variable; **LOS** – Length of Stay; **MA** – maximum amplitude; **MD** – mean deviation; **Mg**- Magnesium; **MT** -Massive Transfusion; **N**-number of studies; **n**- number of participants; **Phos-** Phosphorus; **PICU** – Pediatric Intensive Care Unit; **Plts**- platelets; **Pt** – Patient; **PTH** – Parathyroid hormone; **TEG** – thromboelastograph; **VA** – venoarterial; **VV** – venovenous; **yrs**- years

Citation	Theory/Conceptual Framework	Design/ Method	Sample/ Setting	Major Variables & Definitions	Measurement/ Instrumentation	Data Analysis	Findings/ Results	Level/Quality of Evidence; Decision for practice/ application
MacKay et al. (2017). Abnormal calcium levels during trauma resuscitation are associated with increased mortality, increased blood product use, and greater hospital resource consumption: A pilot investigation. No conflict of interest or funding: US	Not stated, implied physiologic regarding citrated blood administration in massive transfusion	Retrospective cohort from single center	n=41 adult trauma patients with MT with measured Ca	IV= Ca during MT DV= mortality	Ca, Injury Severity Score, amt blood products, mortality	Fisher exact, Wilcoxon rank sum, Mann-Whitney, multivariable logistic regression	Hypercalcemia associated with increased mortality, mortality greatest in pts with large volumes of blood products and Ca deviations; 85 % had hypocalcemia; 22% had hypercalcemia; extreme hypocalcemia had 60% mortality; extreme hypercalcemia had 78% mortality; Pts with both had 75% mortality	Level III, retrospective cohort Correcting Ca in MT may improve survival; small to moderate sample size, adult population, poor outcomes associated with Ca derangements
Mahmood et al. (2018). Current trends in neonatal ECMO. Funding and conflict not mentioned. Authors all from US.	Not stated; implied that many factors influence the decreasing survival of neonates on ECMO	Sweeping review of Neonatal ECMO, indications, survival, equipment	ELSO data up until July 2017	Neonatal respiratory disease, cardiac disease, ECMO equipment, complications, complications, developmental outcomes	Comparing data prior to 2000 with data from 2000-2016	Not described	Neonatal ECMO cases are down trending, survival for cardiac indications improving; overall ECMO survival since 2012 decreasing (83% vs 80%); survival to discharge decreasing (72% vs 67%)	Level V- meta-synthesis; ECMO being offered to increasingly complex Pts, Pt and mechanical complications down trending, morbidity remains high. Efforts to reduce complications will further improve outcomes
Mok et al. (2016). Neonatal extracorporeal membrane oxygenation:	Not stated, implied changing technology will change outcomes	Sweeping review of innovations, and discussion	Clinical trials from MEDLINE and Cochrane Library using key words	ECMO technology described, anticoagulation discussion,	Discussion based on relevant trials to each area of	Not described	Fewer neonates with respiratory failure go on ECMO, patients are more complex and	Level-V meta-synthesis; Centers who offer ECMO need to prepare for

Key: **AKI** – Acute kidney injury; **aPTT**- activated partial thromboplastin time; **Ca** – Calcium; **iCa**- Ionized Calcium; **DV**-dependent variable; **ECMO** – Extracorporeal Membrane Oxygenation; **EBT**- Exchange Blood Transfusion; **ICU** – Intensive Care Unit; **IV**- independent variable; **LOS** – Length of Stay; **MA** – maximum amplitude; **MD** – mean deviation; **Mg**- Magnesium; **MT** -Massive Transfusion; **N**-number of studies; **n**- number of participants; **Phos-** Phosphorus; **PICU** – Pediatric Intensive Care Unit; **Plts**- platelets; **Pt** – Patient; **PTH** – Parathyroid hormone; **TEG** – thromboelastograph; **VA** – venoarterial; **VV** – venovenous; **yrs**- years

Citation	Theory/Conceptual Framework	Design/ Method	Sample/ Setting	Major Variables & Definitions	Measurement/ Instrumentation	Data Analysis	Findings/ Results	Level/Quality of Evidence; Decision for practice/ application
Update on management strategies and long-term outcomes. Authors state no conflict of interest. Funding not mentioned: Singapore and US	for critically ill neonates	of long-term outcomes	ECMO, neonate, outcomes	blood products, cooling, nutrition, and ECMO team	emphasis in the review		have longer ECMO runs, survivors of neonatal ECMO have neurodevelopmental and respiratory morbidities; mortality risk factors include younger gestational age, low birth weight, pre-ECMO acidosis, age of initiation greater than 7 days, VA ECMO, complications	increased Pt complexity Emphasize neurodevelopmental follow up for neonates who underwent ECMO.

Key: **AKI** – Acute kidney injury; **aPTT**- activated partial thromboplastin time; **Ca** – Calcium; **iCa**- Ionized Calcium; **DV**-dependent variable; **ECMO** – Extracorporeal Membrane Oxygenation; **EBT**- Exchange Blood Transfusion; **ICU** – Intensive Care Unit; **IV**- independent variable; **LOS** – Length of Stay; **MA** – maximum amplitude; **MD** – mean deviation; **Mg**- Magnesium; **MT** -Massive Transfusion; **N**-number of studies; **n**- number of participants; **Phos-** Phosphorus; **PICU** – Pediatric Intensive Care Unit; **Plts**- platelets; **Pt** – Patient; **PTH** – Parathyroid hormone; **TEG** – thromboelastograph; **VA** – venoarterial; **VV** – venovenous; **yrs**- years

Table A2

Synthesis Table

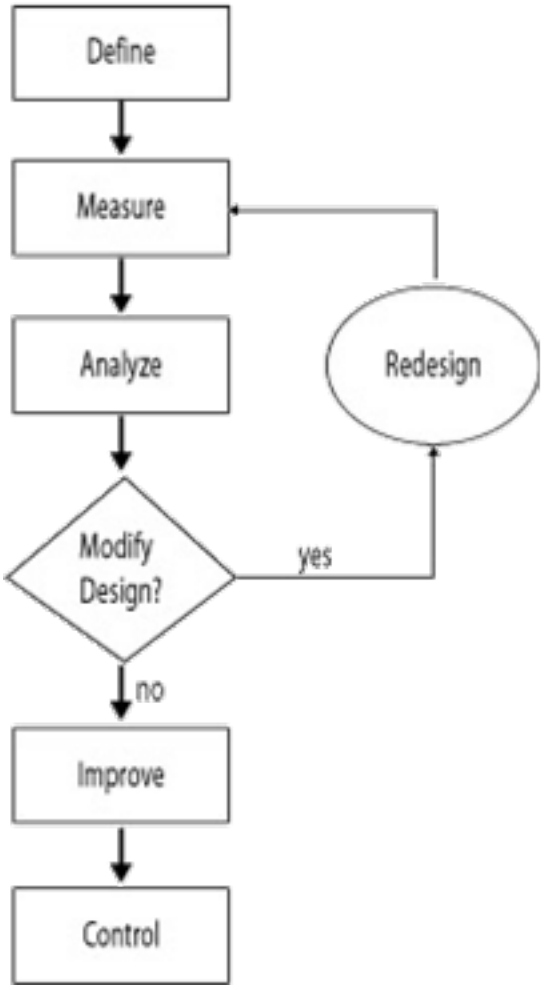
Study	Giancarelli	Ogunlesi	Rambaud	Ho	Kaplan	Church	Schueller	MacKay	Mahmood	Mok
Level of Evidence	III	I-unable to complete	III	III	III	III	III	III	V	V
Study Size	156	1	11	610	78	752	268	41	NA	NA
Population	Adult	Neonate	Neonate	Adult	Neonate/Pediatric	Neonate	Neonate	Adults	Neonate	Neonate
MBT	Y	Y- EBT	N	Y	N	N	N	Y	N	N
ECMO	N	N	Y	N	Y	Y	Y	N	Y	Y
Ca or iCa	Y	Y	Y	Y	Y	N	N	Y	N	N
Risk factors for Ca Derangement	MBT	EBT	ECMO	Critical bleeding Coagulopathy	Younger ↓ weight ↑ creatinine	NA	NA	Severe injury ↑ volume blood products	NA	NA
Findings Associated with Ca Derangement	↑ aPTT ↑ lactic ↓ Plts ↓ pH	NA	NA	↓ clot strength	↑ ECMO duration ↑ hospital LOS ↑ ICU LOS ↑AKI	NA	NA	↑ volume blood products	NA	NA
Ca Derangement and Mortality	↑ mortality with abnormal Ca	No difference	NA	NA	No difference	NA	NA	↑ mortality with ↓ Ca	NA	NA
Other Mortality Risk Factors Identified	NA	NA	NA	NA	NA	CDH Acidosis ICH CI	AKI Postnatal Age 7-13 days VA ECMO	Total units of blood products administered	NA	↓ Gestational age ↓ Birth weight Acidosis Age of initiation greater than 7 days VA ECMO Complications

Key: **AKI** – Acute kidney injury; **aPTT**- activated partial thromboplastin time; **Ca** – Calcium; **CDH**- Congenital diagrammatic hernia; **CI**- Cerebral infarct; **ECMO** – Extracorporeal Membrane Oxygenation; **EBT**- Exchange Blood Transfusion; **ICH**- Intracranial Hemorrhage; **ICU** – Intensive Care Unit; **LOS** – Length of Stay; **MA** – maximum amplitude; **MD** – mean deviation; **Mg**- Magnesium; **MT** -Massive Transfusion; **N**-number of studies; **n**- number of participants; **Phos**- Phosphorus; **PICU** – Pediatric Intensive Care Unit; **Plts**- platelets; **Pt** – Patient; **VA** – venoarterial; **VV** – venovenous

Appendix B

Framework

DMAIC Framework



(*DMAIC Process: Define, Measure, Analyze, Improve, Control*, n.d.)

Appendix C

Table 1

Frequency Table for Nominal Variables

Variable	Calcium Gluconate	Calcium Chloride
ECMO Team Age Category		
Pediatric	23 (85%)	20 (69%)
Neonatal	4 (15%)	9 (31%)
Categorical Indication for ECMO		
Cardiac	20 (74%)	13 (45%)
Sepsis Resp	1 (4%)	0 (0%)
Resp	5 (19%)	12 (41%)
Sepsis	1 (4%)	1 (3%)
Arrest	0 (0%)	3 (10%)
Outcome		
Expired	10 (37%)	7 (24%)
Survived to Discharge	11 (41%)	15 (52%)
Survived ECMO, Expired	6 (22%)	7 (24%)
ECPR		
Yes	11 (41%)	11 (38%)
No	16 (59%)	18 (62%)
CRRT		
No	21 (78%)	21 (72%)
Yes	6 (22%)	8 (28%)
Mode		
Veno-Arterial	25 (93%)	23 (79%)
Veno-Venous	2 (7%)	5 (17%)
Ven-Venous converted	0 (0%)	1 (3%)

Note. Due to rounding errors, column wise percentages may not equal 100%.

Table 2

Summary Statistics Table for Interval and Ratio Variables by Calcium

Variable	*M*	*SD*	*n*	SE_M	Min	Max	Skewness	Kurtosis
Kg								
Calcium Gluconate	6.11	2.44	27	0.47	3.00	10.40	0.48	-1.08
Calcium Chloride	5.55	2.22	29	0.41	2.15	10.47	0.64	-0.63
ECMO patient days								
Calcium Gluconate	7.11	5.24	27	1.01	2.00	20.00	1.24	0.62
Calcium Chloride	8.52	6.51	29	1.21	2.00	35.00	2.44	7.51
Hospital length of stay								
Calcium Gluconate	111.96	92.13	27	17.73	16.00	348.00	0.95	-0.01
Calcium Chloride	77.41	88.10	29	16.36	2.00	348.00	2.05	3.82
Age at ECMO Initiation								
Calcium Gluconate	176.93	73.68	27	33.42	6.00	605.00	1.26	0.54
Calcium Chloride	155.52	183.88	29	34.15	1.00	545.00	1.11	-0.29

Note. '-' indicates the statistic is undefined due to constant data or an insufficient sample size.

Table 3

Two-Tailed Mann-Whitney Test for Post-ECMO ionized calcium by Groups

	Mean Rank				
Variable	calcium gluconate	calcium chloride	*U*	*z*	*p*
Post-ECMO ionized calcium	25.69	31.12	315.50	-1.25	.213

Table 4

Observed and Expected Frequencies Fisher's Exact Test

	Calcium			
Post-ECMO ionized calcium	calcium gluconate	calcium chloride	OR	*p*
Outside	20[15.91]	13[17.09]	3.43	.033
Inside	7[11.09]	16[11.91]		

Note. Values formatted as Observed[Expected].

Figure 1

Boxplot of Post ECMO ABG VBG ionized calcium by calcium gluconate vs calcium chloride