Platelets Count During Circulatory Assistance: Involvement in the Changes of Oxygenation Membrane

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Abstract: Background To study the evolution of platelet count during patient treatment with Extra-Corporeal Membrane Oxygenation (ECMO) and the causes of Membrane Oxygenation (MO) exchange. Assessment of the morbidity and mortality rate was our secondary objective. Methods A single center retrospective study was conducted from January 2014 to December 2015. One-hundred and thirty-nine MO exchanges were studied over 73 patients who received 66 MO exchange. Alterations in biological parameters were compared before and after each MO exchange, to study the device-related platelet count evolution. Results Mean patient age was 56.8±13.4 years. The mean duration of the MO was 5.9±3.1 days, exchanged 26 times (68%) after clot formation. The median Survival After Veno-arterial ECMO score (SAVE score) was -3.5 [-4; -1] interquartile range [IQR]. The median Respiratory Extra-corporeal membrane Oxygenation Survival Prediction score (RESP score) was -1 [-3; 0] [IQR]. A significant decrease (p<0.001) in platelet count between the first and second MO exchange was observed in comparison with the baseline. Yet a steady decline was noted after the third MO exchange, afterwards, normalization was observed after ECMO weaning. During ECMO, a decrease in platelet count from the baseline was found after the first MO on day 2 (p<0.001), the delta was 58.000±19.000 //μL, followed by an additional significant decrease on day 3 (p=0.001). The average platelet transfusion was 0.6±1.4 units. Interestingly, the more MO was exchanged, the lesser blood products transfusion was done. The overall mortality rate was 39%; in Veno- Arterial ECMO (VA-ECMO) it was 34.48% and 41.38% in Veno-Venous ECMO (VV-ECMO). Conclusion Clot formation is the leading cause of MO exchange during ECMO. Therefore, there is a significant decrease in platelets count starting from day 2 that indicates platelets transfusions in order to prevent complications of hemostasis.

Keywords: Platelets, Membrane Oxygenation, ECMO, ECLS, SAVE Score, RESP Score, Cardiac Surgery

1. Introduction

Over the last 47 years, Extra-Corporeal Membrane Oxygenation (ECMO) and Extra-Corporeal Life Support (ECLS) have emerged as techniques providing both cardiac and respiratory support [1].

According to Extracorporeal Life Support Organization (ELSO), ECLS stand for Veno-Arterial ECMO (VA- ECMO) and ECMO for Veno-Venous ECMO (VV-ECMO) [2].

Many deaths occur in the first 3 months after the discontinuation of ECMO. On the other hand, those who survive the initial critical period after ECMO seem to have a longer life expectancy, especially if treated for an infectious disease [3]. Membrane Oxygenation (MO) complication

events during ECMO have decreased in recent decades due to improved coatings and biocompatible materials [4, 5].

Technical complications remain critical during ECMO therapy representing 30% of all ECMO treatments. Forty-five percent of system exchanges had to be conducted urgently, whereas the remaining percentage could be performed electively. Maintaining a platelet count of greater than 200.000 //µL, results in decreased overall bleeding complications, without increasing morbidity or mortality [6].

In 10% of cases there were unpredictable mechanical complications and in 5% a suspected infection of the device which was a rare complication requiring a system exchange [7]. Eighty five percent of technical complications caused by clot formation in the MO affect the gas transfer and device-related coagulation disorder. The ECMO pump can cause hemolysis. Controlling the gas exchange capability and the pressure drop across the MO, as well as monitoring of coagulation and hemolysis parameters over time, allow earlier identification of these complications ultimately reducing emergency exchanges [7].

Many complex factors interact to control hemostasis; the platelet number and function has a significant impact on the development of primary hemostasis. Platelets are consumed and damaged by the artificial circuit and the MO. The use of systemic anticoagulation and the onset of circuit-related thrombocytopenia contribute to the increased incidence of hemorrhagic complications during ECMO, significantly affecting the average platelet count, administration of platelets and bleeding complications [6].

If the platelet count is less than 20,000 //µL spontaneous bleeding can occur. The usual practice is to transfuse platelets (adherence to the MO) to keep the count greater than 80,000//µL. Even though the platelet count is over 80,000//µL, platelet functions may be impaired [2].

2. Materials and Methods

The present study was conducted at the university hospital of Clermont-Ferrand, Department of Cardiovascular surgery. A non-randomized retrospective study was done from January 2014 to December 2015. The population of study was 87 patients, treated with ECMO by using the Quadrox D (Maquet®, Rastatt, Germany) circuit. Fifty-eight patients had VA-ECMO and 29 VV-ECMO; MO exchange was performed 66 times. Fourteen patients who died under ECMO in less than 48 hours were excluded.

Among the patients who benefited from multiple MO exchanges, we studied only the first four MOs (First MO built-in ECMO and the next three MO exchanges), knowing that the maximum exchange number was 6 times. The total number of MOs studied was 139 (figure 1).

All MO exchanges were performed by highly trained team including Cardiac surgeon, ECMO perfusionist and practitioner nurse.

Two scores have been used to predict the survival rate developed by ELSO. The Respiratory Extracorporeal membrane oxygenation Survival Prediction score (RESP) for adult patients undergoing VV- ECMO for respiratory failure and second score is the Survival After Veno-arterial ECMO score (SAVE) which is designed for adult patients undergoing VA-ECMO for refractory cardiogenic shock.

In order to study the evolution of platelet count and its normalization, we compared two-day platelet count results before MO exchange and two days after it. In addition, we continued to evaluate the platelet count five days after ECMO weaning.

We evaluated the association between MO exchanges and alterations in biological laboratory parameter. The exchange procedures were associated with a full examination on daily basis of the circuit, hemolysis, coagulation, and hemostasis parameters. These factors could predict the need for a MO exchange.

This retrospective analysis compared consecutive platelet count on admission and during the total duration of MO to study the device-related platelet count evolutions. According to our ECMO per- procedural protocol for the anticoagulation, we gave unfractionated heparin: bolus 50-100 unit//Kg in the time of cannulation, then continuous infusion (no standard dose; 20-70 u//Kg//h), then Activating Clotting Time (ACT) measured hourly (more frequently if needed), ACT: 1.5 time's normal level. Platelet transfusion was given prophylactically in patients with a platelet count lower than 80,000 //µL or therapeutically in active bleeding, in patient known case of thrombocytopenia or platelet function defect.
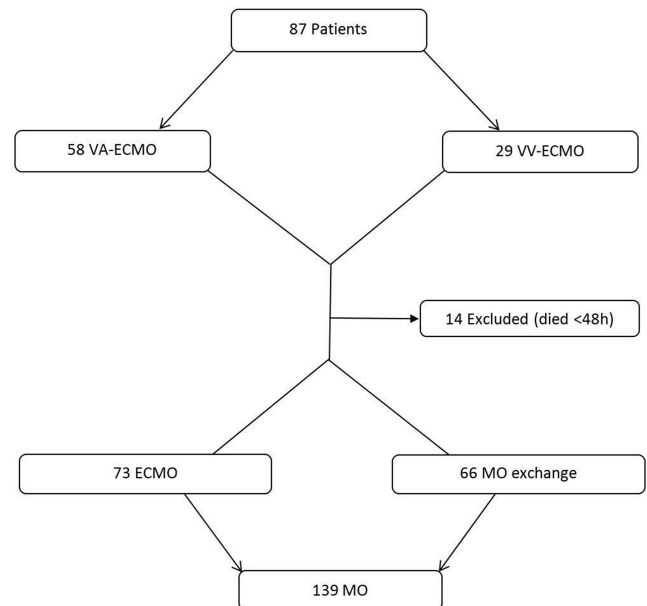
Figure 1. Total number of MO exchange. Legends: VV-ECMO: Veno-Venous ECMO, VA-ECMO: Veno-Arterial ECMO, MO: Membrane Oxygenation.

3. Statistical Analysis

Statistical analysis was performed using Stata software, version 13 (StataCorp, College Station, TX, US). All tests were two-sided with a Type I error set at 0.05. Continuous data were expressed as means±standard deviations (SD) or as

medians with interquartile range [IQR] according to statistical distribution and categorical parameters as frequencies and associated percentages. Comparisons according to patient status (dead or alive) were realized for continuous data by Student t-test or Mann-Whitney test when assumptions of t-test were not met. The normality was studied with the Shapiro-Wilk test and the homoscedasticity with the Fisher-Snedecor test. Concerning categorical data, Chi-squared or Fisher's exact tests were performed. For longitudinal data (platelet count), statistical analysis was conducted with mixed models to take into account the repeated measurements per subject ("subject" random effect) and the time covariate. These models were also adjusted on platelet transfusions. The normality of models' residuals was studied.

4. Results

The mean age was 56.8±13.4 years. In regard to ECMO indications, cardiac insufficiency represented 43.8% (n=32), post cardiotomy 35.6% (n=26), respiratory insufficiency 15.1% (n=11) and septic shock 5.5% (n=4). The median SAVE score of -3.5 [-4; -1] [IQR], RESP score of -1 [-3; 0] [IQR] and EUROSCORE II of 13 [5; 34] [IQR]. The total mortality rate was 27%. The lowest survival rate was for heart failure 45%

(n=32), postcardiotomy 36% (n=26), respiratory failure 15% (n=11), septic shock 5.5% (n=4). All patient characteristics are represented in Table 1.

The procedure of MO exchanges and even the number of MO did not affect the mortality rate, but did in multiple RBC and platelet transfused patients (p value 0.03, 0.02 respectively). The average transfusions rate was: platelet 0.7±1.5 units, red blood cell (RBC) 4.5±6.6 units and fresh frozen plasma (FFP) 1.2±units. In table 2, ECMO and transfusion are described in details.

The incidence of major complications of both the patient and the circuit included renal failure in 26% then tamponade in 20%. The table 3 depicts the incidence of major patients and circuit complications.

The median duration of ECMO was 7 days (IQR: 4 to 11). The mean duration of MO was 5.8±3.2 days, the minimum was less than one day and the maximum duration was 19 days.

Causes of MO exchange were mainly clot formation in the MO 68.4% (n=26); thrombocytopenia with a mean of 36.000±13.000 //μL 15.7% (n=6), switch from VA-ECMO to VV-ECMO 5.3% (n=2), decrease in ECMO flow during weaning test 5.3% (n=2) and 5.3% (n=2) times because of a technical problem with the machine (sudden arrest and noisy pump).

We found a significant drop in the mean platelet count (p<0.001) from the initiation of ECMO to day 2, with an additional significant decrease on day 3 (112.5 ± 56.1 x10^9//L) (p=0.001). The delta of platelet count pre ECMO and day 1 post ECMO was 58.0 ± 19 x10^9//L.

In relation to MO exchange, a significant decrease in average platelet count (p<0.001) was observed between the first and second exchange in comparison with the baseline. Table 4, demonstrates the mean platelet count variations relating to exchange in MO.

Subsequently, we observed a stable decreased platelet count after the third MO exchange. On the other hand, a normalization of platelet count occurred five days after the weaning of ECMO. In figure 2, Pattern of average platelet count along with MO exchange was reported.
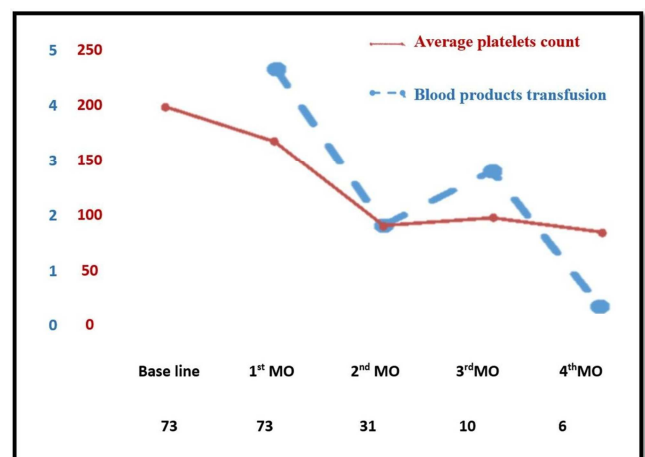
Figure 2. Pattern of average platelet count along with MO exchange. Legends: Ex: Exchange, MO: Membrane Oxygenation.

Table 1. Patient characteristics.

patients	TOTAL	survival	death	p Value
Age (years), mean±SD	56.8±13.4	55.8±14.4	59.3±10.4	0.25
Sex male, n (%)	55 (75)	39 (74)	16 (80)	0.76
Body mass index (kg//m²), mean±SD	27±5	27±5	28±5	0.32
Risk factors:				
· Hypertension, n (%)	43 (59)	31 (59)	12 (60)	0.91
· Non-insulin dependent diabetes, n (%)	16 (22)	9 (17)	7 (35)	0.12
· Insulin dependent diabetes, n (%)	4 (6)	2 (5)	2 (10)	0.30
· Smoking, n (%)	39 (53)	22 (42)	17 (85)	0.001
· Chronic obstructive pulmonary disease, n (%)	7 (10)	4 (8)	3 (15)	0.38
· Dyslipidemia, n (%)	33 (45)	21 (40)	12 (60)	0.12
· New York Heart Association, mean±SD	3.4±0.9	3.3±1.0	3.6±0.7	0.36
· Angina class 4, n (%)	12 (17)	6 (11)	6 (32)	0.07
· Peripheral arterial disease, n (%)	5 (7)	5 (9)	0 (0)	0.32
Comorbidities:				
· Renal failure, n (%)	39 (53)	29 (55)	10 (50)	0.72

patients	TOTAL	survival	death	p Value
· Neurological disorders, n (%)	1 (1)	1 (1)	0 (0)	1.00
· Liver failure, n (%)	3 (4)	2 (4)	1 (5)	1.00
· Respiratory failure, n (%)	11 (15)	6 (11)	5 (25)	0.16
· Heart failure, n (%)	45 (62)	29 (55)	16 (80)	0.05
Cardiac Echography:				
· Left ventricular ejection fraction, mean±SD	37±20	36.8±19.8	38.8±21.8	0.65
· Pulmonary systolic blood pressure, mean±SD	45±17	46.1±17.6	42.7±16.7	0.41
Previous cardiac surgery, n (%)	12 (17)	8 (15)	4//19 (21)	0.72
Recent myocardial infarction, n (%)	17 (25)	10 (19)	7//19 (37)	0.13
Cardio-vascular surgery, n (%)	1 (8.3)	1 (11.1)	0	0.14
Isolated CABG	4 (33.3)	1 (11.1)	3 (100)	
Valve surgery	2 (16.7)	2 (22.2)	0 (0)	
Aortic surgery				
Valve + aortic surgery	2 (16.7)	2 (22.2)	0 (0)	
Cardiac transplantation	3 (25)	3 (33.3)	0 (0)	
ECMO indication, n (%)				0.95
· Heart failure	32 (45)	22 (41.5)	10 (50.0)	
· Postcardiotomy	26 (36)	20 (37.7)	6 (30.0)	
· Respiratory failure	11 (15)	8 (15.1)	3 (15.0)	
· Septic shock	4 (5.5)	3 (5.7)	1 (5.0)	
ECMO, n (%)				0.69
· Veno-Arterial ECMO	50 (68.5)	37 (69.8)	13 (65.0)	
· Veno-Venous ECMO	23 (31.5)	16 (30.2)	7 (35.0)	
SAVE score (VA ECMO 50//73), median [IQR]	-3.5 [-4; -1]	-2 [-4; -1]	-4 [-5; -1]	0.14
RESP score (VV ECMO 23//73), median [IQR]	-1 [-3; 0]	-1.5 [-3; 0.5]	0 [-2; 0]	0.58
EUROSCORE II, median [IQR]	13 [5; 34]	12 [4; 28]	16 [8; 21]	0.38

Table 2. *Description of ECMO and transfusion.*

total		Survival	Death	P Value
ECMO duration (days), median [IQR]	7 [4; 11]	8 [5; 11]	6 [2.5; 11]	0.21
ECMO, n (%) Central ECMO	27 (37)	19 (36)	8 (40)	0.74
Peripheral ECMO	46 (63)	34 (64)	12 (60)	
MO number, mean±SD	1.7±1.1	1.7±1.0	1.7±1.1	0.58
Average duration of MO (days), mean±SD	5.9±3.1	6.1±3.2	5.2±3.1	0.24
Platelet count, mean±SD	203±87	196±84	224±94	0.27
No. of Red Blood Cell transfusion units, mean±SD	4.5±6.6	3.4±5.5	7.5±8.3	0.03
No. of platelet transfusion units, mean±SD	0.7±1.5	0.5±1.4	1.1±1.9	0.02
No. of fresh frozen plasma transfusion units, mean±SD	1.2±2.7	1.2±2.7	1.1±2.8	0.80

Legends: ECMO: Extra-corporeal membrane Oxygenation, MO: Membrane Oxygenation, SD: Standard Deviations, IQR: interquartile range.

Table 3. *Incidence of complications of patient and circuit.*

Complications of patient and circuit			
Primary complications			**N (%)**
	Hemorrhagic	Bleeding at cannulation site	2 (3)
	Cannula complication	Iliac artery dissection	1 (1)
	Circuit complication	Circuit obstruction	1 (1)
Secondary complications			
		Left ventricular overload	6 (8)
Cannula complication		Distal limb ischemia	5 (7)
		Pseudo-aneurysm	2 (3)
		Harlequin syndrome	1 (1)
		Tamponade	15 (21)
		Pulmonary hemorrhage	4 (5)
Hemorrhagic		Gastrointestinal hemorrhage	4 (5)
		Hematoma of Scarpa	2 (3)
		Cerebrovascular hemorrhage	1 (1)
		Cerebrovascular accident	6 (8)
Thrombosis		Inferior vena cava thrombosis	5 (7)
		Bowel ischemia	3 (4)
		Intra left ventricular thrombus	1 (1)
		Pulmonary	13 (18)
Infection		Cannulation site	4 (5)
		Septic shock	4 (5)
Insufficient perfusion		Renal failure	19 (26)
		Multi-organ failure	12 (16)

Complications of patient and circuit			
Primary complications			**N (%)**
	Other	Hepatic failure	7 (10)
		Compartment syndrome	3 (4)
Total			73 (100%)

Table 4. The mean platelet count and blood products variation relatively to the exchange in membrane oxygenator.

		1st MO		2nd MO		3rd MO		4th MO	
No of patients	73	73		31		10		6	
RBC transfusion, mean±SD		3.2±5.6		1.5±2.0		1.9±3.6		0.3±0.8	
Platelet transfusion, mean±SD		0.5±1.4		0.2±0.6		0.1±0.3		0	
FFP transfusion, mean±SD		0.9±2.4		0.2±0.9		0.8±1.9		0	
Blood products transfusion, mean±SD		4.7±8.6		1.8±2.8		2.8±4.8		0.3±0.8	
		2DB	2DA	2DB	2DA	2DB	2DA	2DB	2DA
Average platelet, mean±SD	203±87	175±76	133±75	105±59	105±69	112±68	135±83	100±61	138±103
P Value[1]	<0.001	0.03		0.85		0.19			

Legends: MO: Membrane Oxygenation, SD: Standard Deviations, RBC: Red blood cell, FFP: Fresh frozen plasma, 2DB: 2 days before MO exchange, 2DA: after MO exchange. P-value[1]: Consicutive comparision of platelets count between every 2 consicutive MO exchanges.

5. Discussion

This retrospective analysis in 73 patients compared consecutive platelet count on admission and during the total duration of the ECMO. It aimed to study the device-related platelet count disorders.

The most common technical complication of ECMO is clot formation [8]. Clot formation in MOs can occur despite adequate anticoagulation that compromises gas transfer to the extent where MO exchange is necessary [9]. Many studies and publications, both domestic and international, have detailed this phenomenon. Researchers hypothesize that it is the activation of platelets that subsequently may cause the deposition of fibrin, enhancing thrombus formation.

According to ELSO, thrombocytopenia is common in ECMO. This correlates with our findings. Circulating platelets adhere to plastic surfaces and undergo a release reaction that attracts other platelets [10].

Removal of the MO resulted in a reduction of D-Dimer levels, delaying increases in fibrinogen concentration and platelet count over the next five days [7].

Robinson et al. reported a mean decrease of 26% in the platelet count after the first 15 minutes of the initiation of ECMO, with an additional mean decrease of 16% by the end of one hour (p < 0.05). The resolution of platelet aggregation abnormalities and normalization of platelet count occurred 8 hours after the weaning of ECMO [10].

This corresponds to our first result, regarding the significant mean decrease in the platelet count from the baseline platelet count found on day 2 after the initiation of ECMO (p<0.001), with an additional significant mean decrease on day 3 (p 0.001). Furthermore, we observed a significant decrease in average platelet count (p<0.001) between the first and second MO exchange in comparison with the baseline.

Then a steady decrease in platelet count was witnessed after the third MO exchange. However, a resolution of platelet count occurred five days after the discontinuation of ECMO.

Using anticoagulation to avoid the formation of clots in the ECMO circuit is mandatory whereas it's important to balance the patient's risk of bleeding. Clots are very dark non-moving areas on the MO surfaces. Large clots on MO require the exchange to obtain the maximum benefit from this membrane. No intervention is necessary unless the white thrombi are greater than 5 mm or growing [2].

Broi et al. [7] resume the causes of system exchanges into acute (mechanical failure, acute clot formation) and elective system exchanges (progressive clot formation and worsening of gas transfer, suspected infection and device-related coagulation disorder).

This corroborates the findings of our study in which the incidence of MO exchange was due to the clot formation of MO, thrombocytopenia, transformation from VA-ECMO to VV-ECMO, failure of ECMO weaning, technical problems with the machine, and mechanical failure of the blood pump. No MOs were exchanged due to the suspicion of infection.

Dornia et al. [11], reported thrombotic clot formation in MO device after 8 days from the onset, and had an average duration of 5.9±3.1 days.

In our experience, bleeding is the most common complication during ECMO because of systemic anticoagulation, thrombocytopenia, and thrombocytopathy. Furthermore, a platelet transfusion was ordered for a patient on ECMO if the platelet count falls below 100,000//μL to prevent generalized hemorrhage. Consequently, platelet transfusion carries risks as well as benefits. Infections due to bacteria or fungal are the most commonly reported complications of platelet transfusions [12].

Blood products transfusion was routinely administered during ECMO. Particularly, MO exchange permitted a clear reduction in platelets and RBC transfusion, yet a less evident of FFP. We hypothesised that RBC and platelets are directly affected by the MO but the FFP need is dependent of the systemic inflammatory response induced by the pump itself.

Hemodynamic management can be particularly challenging. The management of bleeding begins with returning the coagulation status to normal as much as possible. Hemorrhagic complications can occur in up to 35%

during ECMO by affecting the primary hemostasis [6].

Adult ECMO patients with lower Hb require more daily RBC and FFP. According to Ang et al., on multivariate analysis, average daily transfusion of RBC increased with hemoglobin < 7·5 g//dl. An average daily platelet transfusion > 3 units was also associated with increased ECMO duration (p=0·024) [13].

In our study, the average platelet count was $195.8 \pm 84.3 \times 10^9$//L, with an average 0.5 ± 1.4 platelet transfusion associated with high mortality rate (p=0.02). Even with the average number of RBC transfusions at 3.4 ± 5.5, we found the same correlation (p=0.03).

Stallion et al. suggest maintaining a platelet count of greater than 200.000//µL while on ECMO, as it results in overall decreased bleeding complications without increasing morbidity or mortality [6].

On the other hand, if the platelet count is less than 20,000 //µL spontaneous bleeding can occur. The usual practice is to transfuse platelets (adherence to the MO) to keep the count greater than 80,000 //µL. Even though the platelet count is over 80,000 //µL, platelet functions may be impaired [2].

Future studies are needed to validate our results, particularly to investigate how ECMO survivors do in terms of cardio-pulmonary function, cognitive function, and quality of life.

6. Conclusion

The platelets count decreases significantly on day 2 in patients who have being treated with circulatory assistance. Prediction of the need for MO exchange implies circuit checking and the study of hemolysis, coagulation, and hemostasis parameters.

Abbreviation

ACT	Activating Clotting Time
ECLS	Extra-Corporeal Life Support
ECMO	Extra-Corporeal Membrane Oxygenation
ELSO	Extracorporeal Life Support Organization
EUROSCORE II	European System for Cardiac Operative Risk Evaluation II MO Membrane Oxygenation
RBC	Red Blood Cell
RESP score	Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score SAVE score Survival After Veno-arterial ECMO score
VA-ECMO	Veno-Arterial ECMO
VV-ECMO	Veno-Venous ECMO

Declarations

Ethical Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

AA conceived the idea. KA, LC and AA designed the study. AA, AS, ND, CL, BP, KA and LC performed the screening, data abstraction, and risk of bias assessment. AA, KA and LC assessed the quality of evidence and wrote the first draft. All authors reviewed, edited, and approved the manuscript. All authors contributed intellectually to the interpretation and reporting of the results.

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