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Efficacy of levosimendan vs its combination with magnesium sulphate on spinal cord protection in infants undergoing coarctectomy: A randomized controlled study

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ABSTRACT

Background and Objective: Spinal cord ischemia with subsequent paraplegia secondary to aortic coarctation repair procedures is rare, but it has serious consequences that can affect quality of life. Infrared spectroscopy (NIRS) is used for non invasive spinal cord oxygenation monitoring to estimate cord perfusion and detect early cord ischemic changes. Several pharmacological agents have been used to improve cord perfusion, the main action of these agents is to improve regional/systemic perfusion and decrease ICP. In the current study, we studied magnesium sulphate and levosimendan for their vasodilating effect that might improve spinal cord perfusion as part of spinal cord protection.

Methods: Forty two infants undergoing aortic coarctectomy under general anaesthesia were registered in double blinded randomized controlled study, three groups were included; group C received i.v. saline, group L received levosimendan in loading dose 6ug/kg i.v. for 15 minutes then maintenance dose 0.1 ug/kg/min till end of surgery and group M received levosimendan in loading dose 6 ug/kg i.v. for 15 minutes then maintenance dose 0.1 ug/kg/min in combination with magnesium sulphate in loading dose 25 mg/kg i.v. for 15 minutes then maintenance dose 10 mg/kg/hr till the end of surgery. The vital signs and NIRS values assessed before, during and after clamping of aorta.

Results: All baseline demographic data were comparable among all groups except for height (cm), which was significantly lower in Group L compared to Group C ($p = 0.013$). NIRS values were comparable among the three groups throughout experimental protocol except after cross clamp at 20 minutes, where Group M was significantly higher compared to group C ($P = 0.007$).Heart rate, mean arterial blood pressure, total fluid intake, urine output, aortic cross clamp time and surgical time was comparable among all groups, were comparable among 3 studied groups.

Conclusion: Adding magnesium sulphate to levosimendan has showed improvement in spinal cord perfusion during cross clamping as monitored by NIRS when compared to use of levosimendan alone or placebo in coarctectomy operations without affecting hemodynamics.

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Levosimendan; magnesium sulphate; spinal cord protection; coarctation of aorta; near infrared spectrometry

1. Introduction

Aortic coarctation (CoA) is a circumferential aortic tapering distal to the origin of head and neck arteries below the left subclavian artery. However, it may occur in any part of the aorta as well, including the arch of the aorta, the thoracic aorta, rarely the abdominal aorta. It accounts for 5% to 8% of all congenital cardiac disorders [1]. Clinically, infants have a cardiac murmur, congestive heart failure, weak femoral pulsations, and discrepancy of blood pressure readings between the upper and lower limbs. Crossland et al. demonstrated a 92% sensitivity rate for an isolated upper-to-lower extremity BP differential of more than 20 mmHg [2]. Severe obstruction in infancy is the main cause of left ventricular (LV) failure and systemic hypoperfusion. Severe COA may become apparent within 2 to 5 days of life, CHF may occur, shock, acidosis and multiorgan system failure often develop at 8 to 10 days of life [3].

During surgical repair, vascular interruption by cross clamping is a key step to accomplish the procedure, but it can have major drawbacks due to ischemia of distal organs, causing renal failure, ischemic hepatitis, necrotizing enterocolitis and/or paraplegia [4]. Ischemia occurs because of prolonged proximal blockage, an interruption in the collateral blood supply, or insufficient collateral circulation. Paraplegia, although is uncommon, yet is a catastrophic complication secondary to spinal cord ischaemia. The presentation of spinal cord ischemia has a erray of presentations, from asymptomatic to major neurological deficits. Incidence of paraplegia after coarctectomy was stated in

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literature to be around 0.3%-0.4% [5,6]. However, even if it is indeed a rare complication, it affects quality of life and represent a socio-economic burden in future for the children & their families.

Improvement in spinal cord perfusion during aortic surgery relies primarily on either prevention of excitetoxicity or decreasing normal cellular metabolism. Permissive hypothermia, cerebrospinal fluid drainage and using distal aortic perfusion had been previously introduced as cord protection techniques with variable outcomes [7,8]. However, pharmacological techniques for neuroprotection of spinal cord are not widely studied.

Magnesium sulphate (MgSo4) is an *N*- methyl-D aspartate (NMDA) receptor antagonist that has neuroprotection on the spinal cord through calcium (Ca ++) channel blocking and vasodilation effect. On the other hand, Levosimendan is a calcium sensitizer that improves hemodynamic without increasing cyclic adenosine monophosphate (c-AMP) or intracellular calcium concentrations. It has a dual pharmacological effect, positive inotropic action through calcium sensitization and a vasodilatation effect through adenosine triphosphate (ATP) dependent potassium channels which can enhance recovery of reperfusion injuries. Katircioglu, et al. demonstrated in an animal sample that levosimendan protects spinal cord from reperfusion injury after clamping during of the aorta during surgery [9].

Close monitoring for spinal cord perfusion during aortic coarctation repair allows for early intervention and management. Routinely, invasive blood pressure or somato-sensory evoked potentials (SSEP) and MEPs (motor evoked potentials) are used for neuromonitoring of spinal cord during surgery, but they have many problems as their amplitude and latency are affected by halogenated or nitrous-oxide-based agents, change in temperature, hypocarbia and hypoxia. Also, both of them are invasive, need specialist and causes more financial burden and not readily available in emergency situations [10,11].

The fundamental advantage of near infrared spectroscopy (NIRS) technology is its capacity to simultaneously and non-invasively assess blood oxygenation of the brain and somatic tissue by placing sensors on the forehead and the appropriate body region, thus providing real-time data on cerebral and peripheral oxygen saturation and regional oxygen saturation (rSO2) differences.So this allows the clinicians to recognize critical events as they develop and track oxygenation trends over time [12]. It is feasible to identify the oxyhemoglobin fraction using just two wavelengths of near-infrared light.

The NIRS technology depends on light emitting diodes (LEDs) which emit near-infrared light through the skin and bone to the deep tissues, as well as two photodetectors 3–4 cm away from the LEDs. When both detectors are attached to the scalp, they allow selective assessment of cerebral tissue oxygenation, which is also known as spatial resolution [13]. NIRS calculates the quantity of light absorbed by oxyhemoglobin and deoxyhemoglobin according to the amount of the energy absorbed by the scalp and skull bone and the light reflected back to the detectors. The resultant oxyhemoglobin to total haemoglobin ratio shows the tissue's regional blood oxygen saturation index. (rSO2), what sets it apart from finger pulse oximetry and several other conventional vital signs, that it is not affected by pulse, blood pressure, or body temperature. So, rSO2 levels are especially of value when vital signs are inconclusive, for example during cardiopulmonary bypass, deep hypothermic circulatory arrest, shock or cardiovascular arrest, and any restriction of regional blood flow, like arterial clamping [14]. Temperature, PCO2, and local variables will all influence the link between (rSO2) and regional PO2 [15].

Thus, the question is as follows: Does levosimendan alone can play a role in spinal cord protection, whether its combination with MgSO4 can provide additive protective effects versus control group guided by NIRS (INVOS), in infants enrolling in elective surgical management of aortic coarctation. Our hypothesis is that levosimendan in combination with Mgso4 would be superior to levosimendan alone in providing better cord perfusion reflected by NIRS (INVOS).

1.1. Patients & methods

This randomized controlled trial was done between March 2020 and May 2022, after approval from Faculty of Medicine, Cairo University's Research Ethics Committee (MD-223-2019). Prior to patient enrolment, the trial was registered at ClinicalTrials.gov (identifier: NCT04330755, main investigator: Dalia Saad Abdelkader, date of registration: 1 April 2020). Before enrolling in the trial, all patient guardians provided written informed permission.

Forty-two infants (aged 0-12 months) scheduled for elective open correction of aortic coarcatation at Abu elreesh children teaching hospital, were enrolled in the study Infants with significant ventricular dysfunction (Ejection fraction < 40%), heart block, pre-existing CNS disorders or on neurological treatment. Also, patients with spina bifida, meningocele or meningomyelocele and infants with pre-existing lower limb motor or sensory affection were excluded from experimental protocol. and patients whose INVOS values dropped 20 scale values of their pre-induction values after maintenance of anaesthesia and finally patients on prostaglandin infusion and inotropic support (Figure 1).

Infants were randomly allocated using computer generated number and concealed using sequentially numbered and opaque sealed envelope and opened

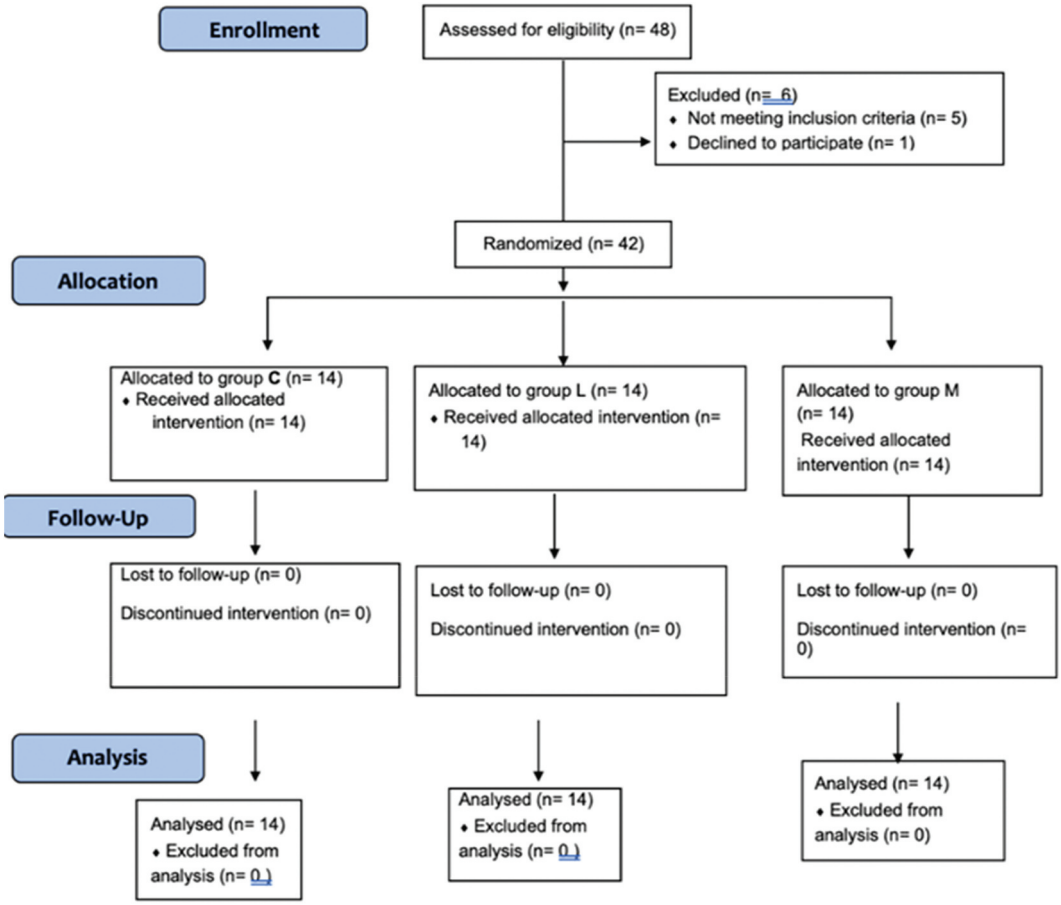

Figure 1. Consort flow diagram of participants.

by anesthesiologist blinded to experimental protocol. Patients were randomly distributed into three groups; Group C (Control group: $n = 14$), Group L (Levosimendan, $n = 14$) and group M (Levosimendan & Magnesium, $n = 14$). Preparation of drugs in all groups were prepared in a fixed volume (50 ml) via clinical pharmacist, and drugs were covered and labelled with patient group, name and method of adminstration, Group (C) 14 patients received saline loading 4 ml/kg over 15 minute and maintenance dose 2 ml/kg/hr. Group (L) 14 patients received dose of 6 µg/kg over 15 min period, followed by intravenous infusion at 0.1 µg/kg/min. 3. Group (M) 14 patients received in separate syringes; a dose of 6 µg/kg levosimendan (Simenda) (Indiamart)over 15 min period, followed by 0.1 µg/kg/min as infusion till the end of surgery and 25 mg/kg magnesium sulphate (Magnisol) (Memphis-Egypt) over 15 min followed by 10 mg/kg/hr magnesium sulphate as infusion.

All enrolled patients were premedicated in the preparation room with 0.2 mg/kg midazolam and atropine 0.02 mg/kg intra-muscularly 20 min before induction of anaesthesia with continuous monitoring of heart rate, oxygen saturation and non invasive blood pressure. Upon arrival to the operating theatre, all patients were placed on a warming thermo blanket and monitored for pulse oximetry (SO2%), 5 lead ECG, non-invasive arterial blood pressure (mmHg) and temperature. Near infrared spectroscopy (INVOS system) (Somanetics, Medtronic) sensors were applied. rSO2-C sensor was put across the middle of the forehead, and the rSO2-S sensor was positioned on the back, with the free end towards the spine and the connector end towards the flank, in the thoraco-dorsal (*T*-10 – L2) region. Bi-spectral index (BIS) leads were applied on the forehead of all patients. Anesthesia was standardized for all patients included in the study. Induction was in the form of 2 µg/kg fentanyl, midazolam 0.1 mg/kg IV. Pancuronium 0.1 mg/kg was given to enable the endotracheal intubation.

Anesthesia was maintained using a mixture of sevoflurane 1.5–3% in oxygen and air (1:1) aiming to maintain BIS measurement between (40–60). Pancuronium (0.01 mg/kg IV) was given for maintaining neuromuscular blockade after insertion of the I.V. cannula. Pressure controlled ventilation (PCV) was adjusted to maintain PaCO2 between 30–35 mmHg. A supplemental dose of 2 µg/kg fentanyl at time of skin incision, retractor application & coarctectomy, was given for analgesia. Two arterial cannulas were inserted according to our protocol (right radial and femoral arteries). Ultrasound guided central venous lines were inserted (internal

jugular or femoral vein). Nasopharyngeal temperature probe and urinary catheter were applied for all patients. Venous samples had been taken for activated clotting time (ACT) before and after heparin (20 i.u/kg) administration during the procedure.

Demographic data collected: Age, sex, weight and height,the duration of cross clamping, heart rate (HR), mean arterial blood pressure (MABP), Spo2, Nasopharyngeal temperature and NIRS values were recorded. T0: immediately before induction of anaesthesia. T1: after maintenance of anaesthesia (when BIS value between 40–60) T2: immediately before aortic cross clamping. T3 and T4: 10 min and 20 minutes following aortic cross clamping respectively. T5: at the end of the surgery.

1.2. Statistical analysis and sample size

In a previous investigation [16] the mean change in rSO2 after cross clamping was −24 ± 6. We calculated our sample size to detect a mean difference of 25% (i.e 6.25) in rSO2 between study groups. Using MedCalc Software version 14 (MedCalc Software bvba, Ostend, Belgium), a minimum number of 30 patients were required to achieve a study power of 80% and alpha error of 0.05 and to conduct comparisons between both control and treatment groups, an adjusted P (Bonferroni correction) of 0.025 was judged significant for the primary outcome, and the sample size that was needed increased to 39 patients (13 patients per group). In order to compensate for probable dropouts, the number was increased to 42 patients (14 patients each group).

Quantitative data were expressed as mean ± SD and qualitative data were expressed as absolute number or percentage and range. Repeated measure ANOVA was used to compare data among all groups, where groups C, L & M were the independent variables and time interval is the dependant variable, if statistical significance was detected a Tukey post hoc test was performed to identify level of significance. The percentage of categorical variables were analysed using the Chi-square or Fischer exact test, if appropriate. P-value <0.05 was considered statistically as significant. Data was analysed using statistical package SPSS 26.0 for windows (SPSS Inc., Chicago, IL, USA).

2. Results

The 42 patients had completed the experimental protocol, where group C is the control group($n = 14$), Group L is levosimendan group ($n = 14$) & Group M is magnesium sulphate and levosimendan group ($n = 14$). Figure 1.

Demographic data is represented in Table 1. Age (months), weight (Kg), Gender (Male: Female) were comparable among the three groups. The height (cm) of patients among levosimendan group was significantly lower compared to control group (p = 0.013) but was comparable to Group M (P = 0.11). Also, height(cm) was comparable between control group and magnesium levosimendan group. NIRS values (rspo2) are presented in Table 2. Values are presented as mean± SD, p value ≤ 0.05 is considered statistically significant T0: before induction of anaesthesia. T1: after maintenance of anaesthesia (when BIS value is between 40–60) T2: immediately before aortic cross clamping. T3.and T4: 10 min and 20 minutes after aortic cross clamping respectively. T5: at the end of the surgery.

Regarding hemodynamics, heart rate and mean blood pressure the results were comparable between the studied groups through all time points.

Oxygen saturation, temperature, total fluid intake and urine output were comparable among all groups, also Aortic cross clamp time and surgical time were comparable among 3 studied groups.

3. Discussion

The main finding of our trial had demonstrated potential beneficial cord perfusion effects of using mix of levosimendan and magnesium sulfate as reflected by NIRS specially at 20 minutes after clamping at (T4).

With underdeveloped collateral circulation, paraplegia is a serious postoperative complication after coarctectomy specially in neonates and young infants. Keen in his study examined 5492 patients with aortic coarctation repair and found the incidence of paraplegia to be around 0.3%. Important interventions for spinal cord protection during aortic procedures are directed to improve spinal cord perfusion mainly by raising proximal blood pressures to improve distal perfusion. Therefore, it is crucial to monitor spinal cord perfusion all through procedure especially during cross clamping time [17]. In our study, group C showed decline in NIRS

Table 1. Demographic data.

	Group c $n = 14$	Group l $n = 14$	Group m $n = 14$	P value
Age (months)	5 ± 3.71	3.62 ± 3.78	4.2 ± 3.46	0.609
Weight (kg)	5.39 ± 2.37	4.89 ± 2.35	5.53 ± 1.86	0.723
BMI (kg/m^2)	12.97 ± 2.9	15.77 ± 5.58	14.86 ± 2.38	0.176
Gender (male: female)	11: 3	12: 2	11:3	0.857

Data are presented as mean ± standard deviation (SD).
Body mass index (BMI) = Body weight(kg)/Height square (m2).

Table 2. Mean ±SD for NIRS values (rspo2) throughout experimental protocol.

	Group C	Group L	Group M	P value
T0	57.43 ± 17.53	56.86 ± 17.67	60.07 ± 16.7	0.872
T1	78.86 ± 11.25 ŧ	78.5 ± 9.47‡	79.07 ± 11.7§	0.99
T2	79.57 ± 9.11 ŧ	79.5 ± 11.95‡	78.86 ± 12.94§	0.984
T3	62.86 ± 17.1	67.07 ± 15.59	73.71 ± 14.15	0.194
T4	62.00 ± 19.18	76.86 ± 16.69	82.35 ± 13.25§	0.007*
T5	88.57 ± 9.4 ŧ	89.79 ± 9.37‡	92.07 ± 4.14§	0.511

Values are presented as mean± SD, p value ≤ 0.05 was considered statistically significant.
T0: before induction of anaesthesia.
T1: after maintenance of anaesthesia (when BIS value is between 40–60)
T2: immediately before aortic cross clamping.
T3.and T4: 10 min and 20 minutes after aortic cross clamping respectively.
T5: at the end of the surgery.
* Denotes significance between rspo2 reading in Group M to Group C.
ŧ Denotes significance between rspo2 reading in Group C.
‡ Denotes significance between rspo2 reading in Group L.
§ Denotes significance between rspo2 reading in Group M.

readings after cross clamping and improved markedly after aortic clamp release which was similar to what Berens RJ.et al found in their study. They concluded that monitoring rSO2-S offers real-time trend data of regional oxygenation distal to the aortic cross-clamp. The deterioration in rSO2-S during aortic cross-clamp was abrupt and critical in most neonates and young infants less than 1 year old, which can be explained by the lack of adequate collateral blood supply to the monitored regional tissue [16].

Similarly, Erin A. Booth et al. [18] in 2010 reviewed cerebral and somatic venous oximetry in both infants and adults, they mentioned the accurate sensitivity of NIRS to monitor cerebral and somatic tissues perfusion in children during cardiac surgery and in the critical care unit (ICU).Likewise, in our study, in group C NIRS readings during clamping time decreased at 10 minutes after clamping (T3), at 20 minutes after clamping (T4) then the reading improved at the end of operation after repair of aorta (T5). In 2013, Etz et al. [19] followed NIRS readings in 20 patients who underwent open thoraco-abdominal aortic aneurysm (TAAA) repair and hybrid repair. Post-cross clamping, the rSO2 readings of individuals who had developed paraplegia were considerably lower than those of patients who did not suffer from neurologic impairment.

By comparing motor evoked potential (MEPS) and NIRS as monitors, Boezeman RP. et al demonstrated that with different spinal cord protection methods (cooling, staged aortic clamping, and partial bypass) in adults with thoracoabdominal aortic aneurysm (TAAA), spinal cord ischemia risk ranges from 3.9% to 13.2% in specialized centres.

NIRS was reliable monitoring for spinal cord perfusion during repair of aneurysm and comparable with motor evoked potential (MEP). That's because anaesthetics and peripheral ischemia do not affect the spinal cord measurement in NIRS as opposed to MEP [20].

Some studies were performed to evaluate the effect of many drugs such as barbiturates, opiates, allopurinol and magnesium sulphate, activated protein C, adenosine, steroids, and volatile anaesthetics. Most of which had promising results from the laboratory and animals' experiments. The neuroprotective drugs could be administered intravenously or intrathecally either prophylactically or after established ischemia and reperfusion of the spinal cord [21].

We also found in this study that levosimendan alone or in combination with magnesium sulphate did not possess hemodynamic drawbacks as reflected by stable MAP & HR compared to control group like the study done by Bravo et al [22] where improvement in cerebral blood volume, intravascular oxygenation as well as global hemodynamic improvement in infants with low cardiac output state refractory to conventional treatment. Levosimendan was tolerated when given as a continuous infusion and by increasing the dose gradually from 0.1–0.2 microgram per kg per min, though they avoided loading dose to reduce the risk of previously reported unfavourable side effects, specifically, hypotension, In agreement to our current study, hypotension was not recorded even with loading doses of Levosimendan alone and even when levosimendan was added to magnesium. Kivikko and his collegues demonstrated that higher doses of levosimendan acts as a phosphodiesterase III inhibitor, activates ATP-sensitive potassium channels in mitochondria, which has a major role in protecting myocardial and other cells against ischemia/reperfusion injury [23].

In our trial, MAP & HR were comparable among all groups throughout the experimental protocol, though hypotension and arrhythmias are the most common drawbacks of levosimendan specially following loading doses. However, this was not the case in our trial, and we can attribute that to numerous factors. In the current trial levosimendan was primarily used prophylactic in hemodynamically stable patients, Wang et al [24] demonstrated that incidence of hypotension and arrhythmias did not differ among levosimendan group and placebo group. Another assumption is that baseline blood pressure is crucial in hypotension as post hoc analysis of SURVIVE trial demonstrated that patients with systolic blood pressure < 100 or diastolic blood pressure < 60 are more prone to mortality [25],

while in the current trial baseline mean arterial blood pressure among all groups were in the range of 80–90 mmHg.

We can conclude from the previously mentioned evidence that hypotension is not always essential among all children receiving loading dose and infusion of levosemindan.

The rationale of our study was that magnesium and levosimendan both have a vasodilator effect, will improve spinal cord perfusion, specially in the narrowed part of the aorta and they might have favourable neurological and hemodynamic action. Furthermore, as shown in multiple animal investigations of spinal cord ischemia, magnesium sulphate has neuroprotective effects. Animal studies have been carried out to determine magnesium's neuroprotective role [26]. The addition of MgSO4 to rat hippocampus slices was discovered to reduce the effect of hypoxia in 1987. McIntosh et al. [27] established in 1989 that MgSO4 injection reduces neurological sequelae in traumatic injuries. Marinov et al. showed in 1996 that administering MgSO4 before a localised ischemia incident in rats could be neuroprotective by inhibiting NMDA receptors [28]. In 2007, Hiroki Kohno, Atsushi Ishida et al. demonstrated study for vasodilator and neuroprotective effect of magnesium as prophylaxis for spinal cord ischemia in rats. They found that the group received MgSo4 showed better recovery and less decline in spinal blood flow during clamping time. this is consistent with our study as group M who received MgSO4 revealed less decrease in NIRS reading when compared to the control group [29].

Since 2004, levosimendan was described to be used in pediatric patients in cardiac operations. Boegli, et al. reported that levosimendan is a safe and promising effective inodilator for prophylactic use in children undergoing cardiac surgery. As we searched related literature, we seldomly found trial that used levosimendan for preconditioning and neuroprotection of spinal cord from ischemia during aortic coarctation repair in pediatric patients. We clearly benefited from the vasodilator feature for enhancing spinal cord perfusion. In our study, in group M (MgSo4 added to levosimendan infusion) showed the most stability in NIRS readings (as part of spinal cord protection during cross clamping period. Also, our results showed that group L (levosimendan) NIRS measurements during cross clamping time were better than the control group. We attributed this finding to the vasodilator action of levosimendan as it improved spinal cord perfusion.

4. Conclusion

Adding magnesium sulphate to levosimendan showed improvement in spinal cord perfusion as monitored by NIRS when compared to use of levosimendan alone, without compromising the hemodynamic of these children.

5. Study limitations

The large size of the probe placed on small sized babies was an obstacle during the study as the use of disinfectant on area of surgery might spilled on the probes. This might interfere with the readings recorded for the study therefore smaller probes are recommended for the future studies on somatic use of NIRS in infants.

6. Recommendations

We recommend recruiting more infants to the future studies as well as follow up in PICU for 24 to 48 hours to better detect the effect of Mg and levosimendan on spinal cord perfusion.We also recommend recruiting adult subjects to a similar study design to better understand the effect of these drugs on adult patients.

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We confirm that we did not use AI or chatGPT in our research in any form.

Disclosure statement

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Declarations

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