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Original research article

EFFECT OF MANNITOL ON ELECTROLYTES AND ITS RELATION WITH KIDNEY INJURY IN CARDIOPULMONARY BYPASS

SALEEM M[1*], AWAN AH[2], MUSHTAQ A[3]

[1]*Department of Cardiac Surgery (Assist. Professor), Punjab Institute of Cardiology Lahore, Pakistan*
[2]*Department of Cardiac Surgery (CPT), Punjab Institute of Cardiology Lahore, Pakistan*
[3]*Department of Cardiac Surgery (Cardiac Perfusionist), Punjab Institute of Cardiology Lahore, Pakistan*
**Correspondence author email address:* drsaleem6001@hotmail.com

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Abstract: *The optimal composition of the priming solution used in cardiopulmonary bypass (CPB) during human cardiac surgery is still uncertain. Mannitol is a common component of CPB priming solutions, but its efficacy is debated. To clarify the effect of mannitol on CPB prime solutions, a prospective, randomized, double-blind trial was conducted on 40 patients with sound cardiac and renal functions who were undergoing coronary artery bypass grafting. The trial included two groups: one received Ringer's acetate-based prime (n = 20), and the other received a combination of Ringer's acetate and 200 mL mannitol as prime (n = 20). The study examined changes in renal-related parameters, electrolytes, osmolality, and acid-base balance. Interestingly, no significant differences in osmolality were observed between the Mannitol and Ringer's acetate groups. However, the Mannitol group showed a significant decrease in sodium levels from 138.7±2.8 mmol/L at the start of anesthesia to 133.9±2.6 mmol/L after the initiation of CPB (p <0.001). Renal parameters remained consistent across groups, except for a temporary effect of mannitol on post-surgery urine output (p = 0.003). In conclusion, this study found no significant differences in osmolality between Ringer's acetate-based prime and Mannitol-based prime in individuals with healthy cardiac and renal function. However, the addition of mannitol to the prime resulted in a significant, albeit short-term, reduction in sodium levels. These findings contribute to the ongoing discourse on optimizing CPB prime solutions, especially in cardiac surgical procedures involving mannitol inclusion.*

Keywords: Mannitol, cardiopulmonary bypass, electrolytes, renal function

Introduction

Cardiopulmonary bypass (CPB) is required for a great deal of patients having cardiac surgery. Preserving equilibrium between acids and bases and adequate electrolyte levels is critical during CPB. (Shann et al., 2006) A CPB circuit prime affects numerous organ systems, including the brain, spinal cord, and the system of kidneys, along with the coagulation process, osmolality, and electrolyte balance; all of this can impact the success of heart surgery.(Liskaser et al., 2009; Liskaser et al., 2000; Maleki et al., 2016; Russell et al., 2004; Shann et al., 2006) However, the selection of CPB prime is frequently influenced by individual tastes and historical ideas. (Lilley, 2002) A recent assessment found significant disparities in CPB procedures and priming worldwide, while the causes for these discrepancies and their influence on clinical results remain unknown. (Miles et al., 2017) There are presently no standards for selecting CPB prime solutions overall or for tailoring a CPB prime to the features and requirements of a single patient.
CPB prime solutions tend to be founded on crystalloid fluids, frequently including mannitol. (Himpe, 2003; Miles et al., 2017) Mannitol functions as a volume expander, has a diuretic-type effect, and may affect several organ systems. According to certain research, taking mannitol may minimize the incidence of postoperative acute renal damage. (Bragadottir et al., 2012; Fisher et al., 1998; Poullis, 1999). Other investigations have found that the creation of acute renal tubular injury has a negative impact on the kidneys.(Fang et al., 2010; Kim et al., 2014; Lin et al., 2015) One research found no influence on clinical results once mannitol was removed from the priming solution, and only financial advantages were seen(Haydock et al., 2014). As a result, there is no clear consensus about the appropriate application of mannitol in cardiac surgery, and only a few studies have been conducted on the effects of utilizing Mannitol in CPB prime solutions. As a result, we devised a prospective, randomized, double-blind trial to assess the impact of mannitol in the CPB prime solution. According to Malmqvist et al., observed plasma osmolality is a more precise technique to detect electrolyte balance than estimated osmolality during CPB and should be included in studies that examine the effect of CPB prime solutions(Malmqvist et al., 2019). Our investigation determined plasma osmolality using the freezing point depression method, an accurate methodology for assessing osmolality.
The main goal of this study was to evaluate the perioperative impact of mannitol in the CPB prime solution to a Ringer's acetate-based prime after cardiac surgery in individuals with healthy pre-operative cardiovascular and renal functioning. We also look into the short-term postoperative outcome, including renal function.

Methodology

This prospective, single-center study was planned as a randomized, double-blind control experiment. The Punjab Institute of Cardiology ethics committee in Lahore acknowledged the study. At the Punjab Institute of Cardiology in Lahore, we enrolled 40 adult patients who were to undergo planned solitary coronary artery bypass grafting (CABG). The researchers informed all patients verbally and on paper before surgery, and a written agreement was acquired for research participation and publication of the results. Randomization was done by non-study clinical personnel who developed the study solution and handed it over to the blinded perfusionist. Normal left ventricle functioning was defined as a pre-operative echocardiography left ventricular ejection fraction of a minimum of 50%, and normal kidney function was defined as an eGFR (estimated glomerular filtration rate greater than 60 mL/min). Patients who weighed less than 50 kg, had a pre-operative hematocrit of less than 24% or had previously undergone heart surgery were excluded. The eGFR in our investigation was calculated as the average of the relative eGFR derived from creatinine and the comparable eGFR derived from cystatin C. To compute eGFR utilizing creatinine, the updated Lund-Malmö formula 19 was used, and for estimating eGFR based on cystatin C, the CAPA-equation 20 was employed.

The Ringer's acetate group (n = 20) was given a 1200 mL priming solution containing 10,000 iu of heparin and 80 mmol of sodium chloride. A priming solution of 1000 mL Ringer's acetate, 10,000 IU heparin, 80 mmol sodium chloride, and 200 mL mannitol was given to the mannitol group (n = 20). Every patient had a median sternotomy to do a standard CABG. Rocuronium was used to promote relaxation, whereas midazolam, fentanyl, and propofol were administered for general anesthesia. Throughout the procedure, fentanyl and propofol were used for sustaining intravenous anesthetic. During CBP, the goal blood pressure range was 40–80 mmHg, and norepinephrine was administered as required. The medical team may provide Ringer's acetate intravenously up to 1000 mL during the procedure. During CPB, heparin was given at a dosage with a minimum active clotting time of 480 seconds. With each patient, the CPB configuration was the same.

The target cardiac index for accepted, non-pulsatile perfusion was 2. 4 L/min/m 2. Throughout CPB, body temperature remained over 36 °C. Cold blood cardioplegia was used to protect the heart. A collection of shed blood was made in the venous reservoir. The day before surgery, pre-operative blood specimens were drawn through the antecubital vein and examined at the hospital's biochemical laboratory. Analysis of pre-and postoperative samples was done. Whole blood was used to test pH and electrolytes. Information was taken from the patient's medical records on the fluid balance during and after surgery, diuresis, and diuretics.

The mean±1 standard deviation was used for continuous data, whereas percentages were used for the categorical variables. The Student's t-test or the Mann-Whitney test was used for continuous data. The chi-squared test was used to compare categorical data. Blood sample changes were compared using the paired-sample t-test. An overall linear model with repeated measurements was employed to examine the primary impact of prime solutions on osmolality, chloride, and sodium levels.

Results

An aggregate of 153 individuals underwent screening. One hundred twelve participants did not match the inclusion requirements, and one patient chose not to participate in the trial. Forty patients were randomly assigned to one of two groups: Mannitol (n = 20) or Ringer's acetate (n = 20). Since all of the patients had coronary ischemia disease, they all had CABG surgery. Table 1 lists the patients' initial features. Before surgery, every single patient had sinus rhythms. Stroke or postoperative disorientation was not expected. Because of postoperative hemorrhage, there was one surgical reoperation in each group. With the exception of the postoperative duration of stay in the intensive care unit, there were no significant differences in the demographic data among both groups. Thirty-day survival was 100 percent. At no point did the Ringer's acetate group and the Mannitol group exhibit appreciable variations in osmolality. When CPB was started (T2), the mean osmolality for all 40 patients increased considerably to 301.9±4.1 mOsm/kg ($p < 0.001$) from 292.5±5.2 mOsm/kg at T1. Between T2 and day 4, all patients had a substantial reduction in their osmolality (301.9±4.1 mOsm/kg and 291.1±5.9 mOsm/kg, respectively) ($p < 0.001$). At any given time, there were no discernible variations between the Ringer's acetate group and the Mannitol group regarding lactate, pH, base excess, bicarbonate, or hemoglobin.

Between the Ringer's acetate and Mannitol groups, mean pre-operative sodium levels were 139.9 ±1.8 mmol/L and 138.7 ±2.8 mmol/L, respectively ($p = 0.104$). Figure 2 A illustrates that there was, nonetheless, a statistically significant difference in the mean sodium level between the two groups from T2 through T6. After beginning CPB (T2), the sodium level in the Mannitol group decreased significantly, from 138.7±2.8 mmol/L at T1 to 133.9±2.6 mmol/L ($p < 0.001$). Between T1 and T2, the sodium level in the Ringer's acetate group was the same (139.9±1.8 mmol/L and 139.3±1.8 mmol/L, respectively; $p = 0.094$). By T2, the total sodium concentration in the Mannitol group was 133.9±2.6 mmol/L; by T6, it had increased to 137.1±2.1 mmol/L ($p < 0.001$). Between T2 and T6, the Ringer's acetate group's sodium levels did not significantly alter (139.3±1.8 mmol/L and 138.9±1.6 mmol, respectively; $p = 0.276$). At any point in time, there were no discernible variations in potassium within both Mannitol and Ringer's acetate groups. The concentrations of potassium within the Mannitol group (3.9±0.4 mmol/L and 4.8±0.5 mmol/L, respectively; $p < 0.001$) and Ringer's acetate group (4.1±0.3 mmol/L and 4.9±0.5 mmol/L, respectively) increased significantly across T1 and T2. Figure 2 shows an essential distinction in average chloride levels across the groups from T2 to T7. In the Mannitol category, there was no significant difference between T1 and T2 (106.5±2.3 mmol/L and 106.8 ±2.4 mmol/L, respectively; $p = 0.272$), while there was a rise in chloride in the Ringer's acetate group among T1 and T2 (107.0±1.8 mmol/L and 111.4±1.5 mmol/L, correspondingly). There were never any clinically significant changes between the Ringer's acetate group and the Mannitol group, according to the data defining the renal function shown in Table 3.

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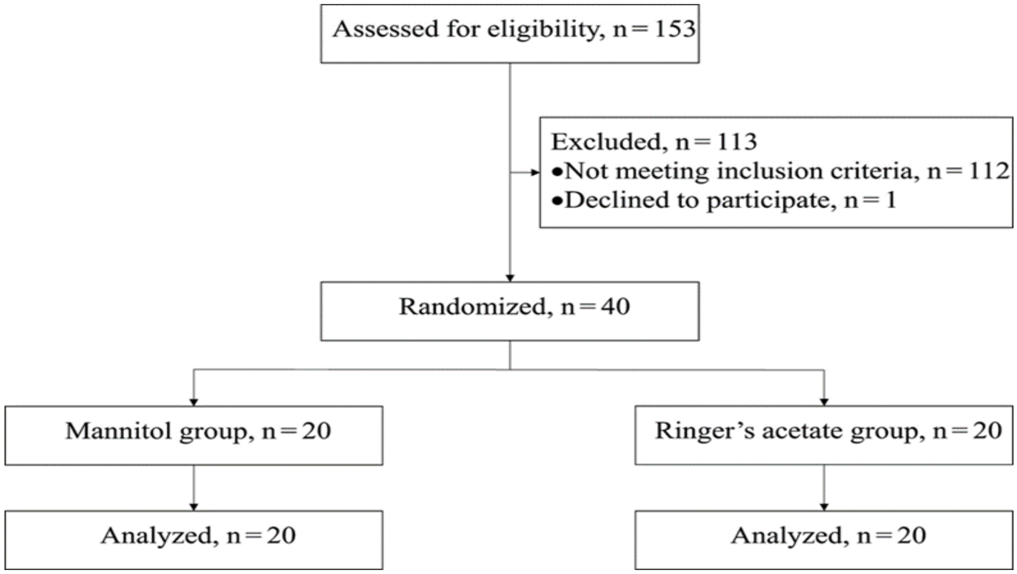

Figure 1. Flow chart of study

Table 1: Demographics of study population

Variable	Ringer's acetate group (n=20)	Mannitol group (n=20)	p-value
Male gender	17(85)	19(95)	1.214
Age (years)	67±9	70±10	0.132
BMI (kg/m²)	26.1±2.4	27.7±2.5	0.645
NYHA class I -II	20(100)	20(100)	
Logistic EuroSCORE I (%)	2.75±1.78	2.45±1.69	0.234
Hemoglobin (g/L)	137.7 ±7.3	138.9 ±9.4	0.975
Creatinine (µmol/L)	79.8±10.1	77.8±12.7	0.916
CPB time (min)	66±20.1	65±19.5	0.654
Cross clamp time (min)	42.2±16	41±12	0.471
Hemofiltration during CPB	0	0	
Pre -/peroperative use of diuretics	0	0	
Peroperative blood transfusions	0	0	
CPB balance (mL)	1299±374	1389±284	0.604
Total peroperative fluid balance (mL)	1842±471	1984±382	0.654
ICU balance at postoperative day 1 (mL)	2479±842	0785±741	0.256
ICU length of stay (hours)	22±4	37±24	0.010
Postoperative AKI	1 (5)	3(15)	0.354

Table 2 indicates the time at which sampling was done along with the sampling site.

Time point	Sampling site	Parameters analyzed
T0. Day before surgery	Peripheral antecubital vein	Creatinine, urea, eGFR, cystatin C
T1. Before the start of the anesthesia	Arterial cannula	Blood gas, plasma osmolality, and Cl
T2. Three minutes following the cardioplegia's delivery	Sample line CPB	Blood gas, plasma osmolality, and Cl
T3. Half an hour after the CPB began.	Sample line CPB	Blood gas, plasma osmolality, and Cl
T4. Hour after the CPB began.	Sample line CPB	Blood gas, plasma osmolality, and Cl
T5. Fifteen minutes following the end of CPB	Sample line CPB	Blood gas, plasma osmolality, and Cl
T6 half an hour after ICU admission	Arterial cannula	Blood gas, plasma osmolality, and Cl
T7. Day 1	Arterial cannula	Blood gas, plasma osmolality, and Cl
T8. Day 4	Central venous catheter	Blood gas, plasma osmolality, and Cl
T9. After three months, CABG	Peripheral antecubital vein	Na, K, Cl, creatinine, urea, eGFR, cystatin C

Table 3: Renal parameters

Variable	Ringer's acetate group (n=20)	Mannitol group (n=20)	p-value
Creatinine (μmol/L)			
T0	78.7±12.3	75.6±12.7	0.174
T6	77.2±15.4	75.1±17.2	0.787
T7	75.4±14.9	72.4±14.0	0.417
T8	85.7±14.8	83.9±17.7	0.466
T9	79.9±11.9	79.5±16.1	0.834
Cystatin C (mg/L)			
T0	0.98±0.14	0.81±0.23	0.254
T6	0.77±0.17	0.92±0.43	0.874
T7	0.75±0.34	0.89±0.83	0.471
T8	1.19±0.76	1.27±0.17	0.245
T9	1.12±0.47	1.04±0.24	0.145
eGFR (mL/min/1.73m²)			
T0	75.2±8.4	87.8±8.7	0.023
T6	79.2±8.5	84.9±7.8	0.089
T7	77.5±9.0	84.4±9.8	0.188
T8	67.4±9.2	72.6±11.5	0.198
T9	71.6±11.7	75.6±11.6	0.288
Urea (mmol/L)			
T0	5.6±1.7	5.2±1.3	0.246
T6	4.8±1.3	4.1±0.8	0.034
T7	4.6±1.3	3.9±0.8	0.077
T8	6.5±2.1	6.3±1.7	0.975
T9	5.8±1.3	5.6±1.4	0.571

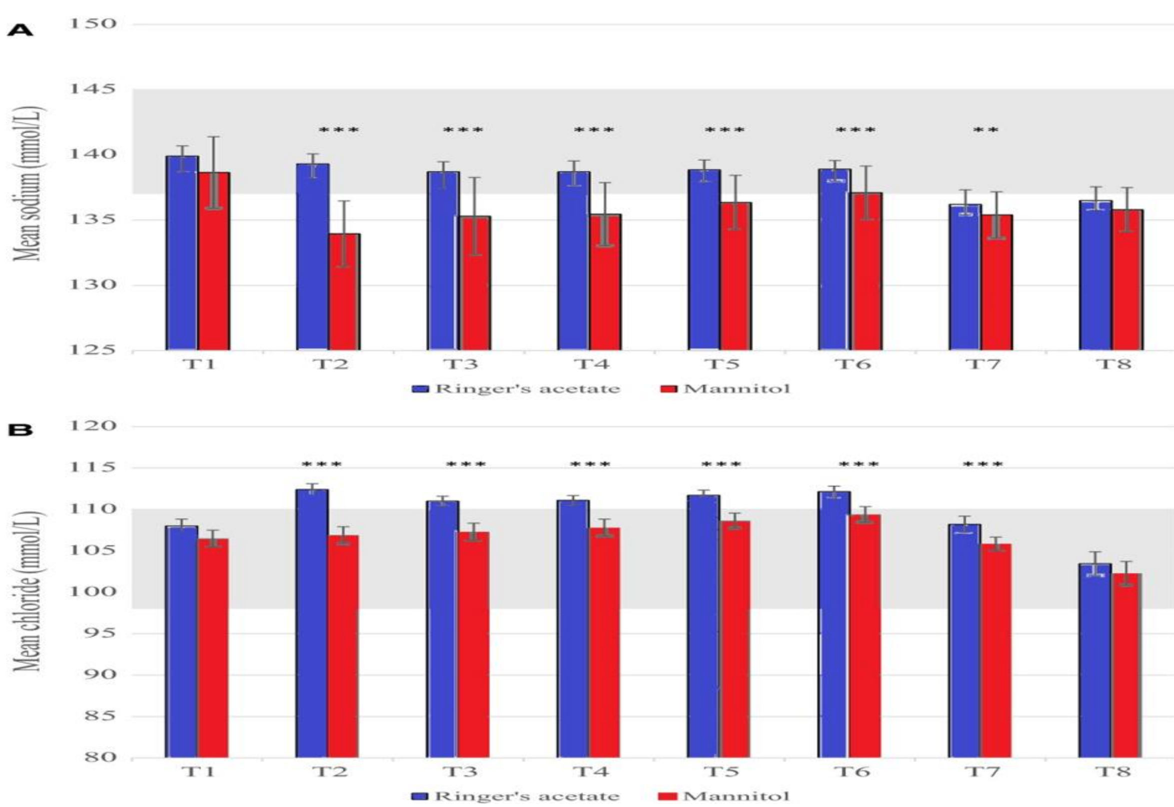

Figure 2 Showing levels of sodium and chloride at different times.(*** p <0.001, ** p <0.01)

Discussion

The study's findings demonstrated that, compared to priming based on Ringer's acetate, the presence of Mannitol in CPB priming solution during a routine CABG had no impact on osmolality, acid-base relationships homeostasis, or kidney health. However, sodium and chloride ranges were significantly lower in the Ringer's acetate group than in the Mannitol group.

The effects of heart surgery on plasma osmolality have not been well studied. It has been noted that using hyperosmolar CPB prime causes a sharp increase in plasma osmolality(Malmqvist et al., 2019), which might harm the central nervous system(King and Rosner, 2010). There is no research in the published literature on the effect of mannitol on the osmolality of plasma after CPB. In neurosurgical circumstances, Manninen et al. have documented an increased osmolality in connection to Mannitol dosage(Manninen et al., 1987)

The current investigation found that mannitol did not influence osmolality compared to a Ringer's acetate-based prime. We discovered that in CABG patients with normal cardiac and renal function, the administration of mannitol in the CPB prime did not affect alterations in osmolality. All the patients' osmolality did, however, rise somewhat during CPB, albeit only marginally over the usual range, and it stayed elevated during the procedure.

This result is consistent with the earlier research conducted by Malmqvist et al. (Malmqvist et al., 2019)

In contrast to the findings of Malmqvist et al., the observed decrease in osmolality in our investigation might be attributed to variations in the prime solutions. The elevated osmolality in our research may also have been caused by the high potassium level of the cardioplegia solution and the substitutional electrolyte therapy administered before and after surgery. However, the alterations in plasma osmolality are transient; by day four following surgery, the osmolality had recovered to pre-intervention values.

Mannitol function in the kidney is debatable. Following heart surgery, renal impairment is a significant consequence that increases mortality and morbidity.(Mangano et al., 1998) Mannitol has been shown to enhance blood flow to the kidneys, which may benefit renal function in cases of acute kidney damage that occur after heart surgery(Bragadottir et al., 2012; Sirivella et al., 2000)

However, a number of studies show that mannitol causes enhanced endothelial cell death and that this might be detrimental in cases of acute renal damage(Malek et al., 1998; Moreira et al., 2017; Zhang et al., 1999)

Carcoana et al. have uncovered the intricate interaction between dopamine and mannitol in individuals receiving CPB. They have shown that this combination raised the microglobulin excretion rate, a sensitive indicator of proximal renal tubular failure.(Carcoana et al., 2003)

Yallop et al. observed no differences in creatinine, water balance, or diuresis between Mannitol and Hartmann's solution in CPB prime(Yallop et al., 2008)

The current investigation found no variations in renal indicators or fluid equilibrium across the groups. Before surgery, the renal function of every patient was expected, and none of them were administered any diuretics. Surprisingly, we observed no change in the groups' postoperative urine production, although the Mannitol group's urine output significantly increased perioperative, suggesting that mannitol affects urine production in the short term. We discovered no discernible advantage to Mannitol in CPB prime in individuals with normal renal function, consistent with the findings of the Yallop et al. trial.

Previous research by Manninen et al. revealed a dose-related drop in sodium after mannitol was administered.(Manninen et al., 1987)

Our data supported these conclusions by demonstrating that, after CABG, the Mannitol group's sodium concentration was noticeably lower. Mannitol inhibits the reabsorption of sodium in the tubules of the kidney in addition to the plasma sodium dilution action, which may lead to the onset of low sodium levels during CBP(Wong et al., 1979)

Research indicates that hyponatremia carries a risk of cerebral edema and is, hence, potentially harmful(Adrogué and Madias, 2000; Crestanello et al., 2013; Munoz III et al., 2014)

The result following heart surgery may be improved by reducing the risk of hyponatremia(Crestanello et al., 2013); in particular, avoiding hyponatremia during CPB is crucial. Using a prime solution devoid of mannitol might help accomplish this objective.

Mannitol has been shown to raise blood potassium levels in a number of trials significantly, but they were conducted outside of heart surgery settings.(Fanous et al., 2016; Hirota et al., 2005)

Between the two groups, there was no discernible change in potassium levels over time. However, due to cardioplegia during CPB and the subsequent substitutional therapy throughout the critical care stay, a rise in potassium was seen in both groups after commencing CPB. More research is necessary to determine the precise impact of mannitol on potassium levels during heart surgery.

There aren't many researches looking at how mannitol affects chlorides. In neurosurgical patients, Manninen et al. observed a drop in serum chlorides when mannitol was used(Manninen et al., 1987)

In contrast to the Mannitol group in our investigation, the Ringer's acetate group had a statistically significant rise in chloride levels during CPB. This change could have been caused by adding more Ringers' acetate to CPB prime instead of mannitol. This finding's therapeutic significance is debatable, especially considering the two groups' equal plasma osmolality.

Our study only includes individuals with normal renal function who underwent CABG surgery and received a maximum of 1000ml Ringer's acetate during perioperative anesthetic fluid therapy. It's unknown how much of the acetate was given to each patient, affecting electrolyte levels. Our randomized clinical trial design is a major strength, allowing us to examine the effects of mannitol in the context of CPB prime after CABG. Using the freezing point depression method to determine plasma osmolality is also a strength.

Conclusion

In individuals with healthy cardiac and kidney function, this prospective, randomized, double-blind trial showed no impact of mannitol on osmolality compared to a CPB prime solution based on Ringer's acetate. There was a noticeable, short-term drop in sodium when mannitol was used in prime. All patients saw a substantial rise in osmolality during CABG, which is thought to be the result of CPB rather than mannitol. Thus, we conclude that more research is necessary to understand mannitol's function in heart surgery fully.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate.
Approved by the department Concerned.

Consent for publication
Approved

Funding
Not applicable

Conflict of interest

Writers have affirmed they have no pending conflicts of interests

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