

when citrulline and placebo groups are compared. Patients receiving study drug showed shorter composite durations of mechanical ventilation and inotrope therapy than did patients receiving placebo. Thus, as assessed by the composite surrogate marker variable, patients receiving study drug were ready for discharge from the PICU sooner than patients receiving placebo. In addition to indicating shorter PICU time, shorter mechanical ventilation time lowers the added risk of physical injury.

[0161] In addition to achieving the targeted plasma citrulline levels, this study also yielded statistically significant and near significant results demonstrating citrulline treatment-dependent differences in the duration of mechanical ventilation and inotrope therapy between the treated and control groups in a small group of 22 subjects.

[0162] The duration of postoperative invasive mechanical ventilation was derived as the time in hours from separation from cardiopulmonary bypass until endotracheal extubation. If a patient required reintubation within 24 hours after extubation, the reintubation time was added in the main analysis. In a second analysis, the reintubation time was not included.

[0163] Including the reintubation time, the mean duration of invasive mechanical ventilation was clearly longer in the placebo group than in the citrulline treatment group, with citrulline-treated patients needing only an average of 5 hours of invasive ventilation while placebo-treated patients needed 37 hours. The difference did not reach statistical significance in the ANOVA test, most likely based on the large variation of durations in the placebo group. However, when the reintubation time was excluded, the difference between the group was still eminent and statistical significance was reached in the ANOVA ($p = 0.0317$). Statistical significance for both analyses was shown by the Wilcoxon rank-sum test. See Figures 20-22.

[0164] Cessation of positive pressure ventilation and inotrope therapy are the two principal determinants of readiness for discharge from the intensive care unit. Together, as a composite variable comprised of the longer of the duration of positive pressure ventilatory support or of inotrope therapy, they can serve as an effective surrogate for the duration of intensive care unit stay. This latter variable is subject to confounding factors that may adventitiously prolong it, such as lack of bed availability.

[0165] In summary, the data from this study shows that the administered dosing regimen achieved the pharmacokinetic endpoint. Further, despite the extremely small sample size of the

Claim

1. A composition for maintaining pulmonary vascular tone in a patient undergoing cardiopulmonary bypass surgery for a cardiac defect comprising:
 - (a) an effective amount of a citrulline bolus formulated to be administered to the patient at the initiation of the surgery;
 - (b) an effective amount of citrulline added to the hemoconcentration replacement fluid used during cardiopulmonary bypass formulated to be administered to the patient during the surgery;
 - (c) a post-surgery citrulline bolus of about 10–30 mg/kg formulated to be administered about 15–45 minutes after decannulation from cardiopulmonary bypass; and
 - (d) an effective amount of citrulline formulated to be infused into the patient after the surgery,
wherein the patient's plasma citrulline level is raised above 100 $\mu\text{mol/L}$.
2. The composition of claim 1, wherein the cardiac defect is selected from the group consisting of a cardiac defect associated with excess pulmonary blood flow, an atrial septal defect, ventricular septal defect, and single ventricle lesion.
3. The composition of claim 1 or 2, wherein the surgery is selected from the group consisting of arterial switch procedure and Glenn and Fontan procedures.
4. The composition of any one of claims 1-3, wherein the bolus of citrulline is 100-300 mg/kg of citrulline.
5. The composition of any one of claims 1-4, wherein 100-300 $\mu\text{mol/L}$ citrulline is added to the hemoconcentration replacement fluid used during cardiopulmonary bypass.
6. The composition of any one of claims 1-5, wherein the effective amount of citrulline formulated to be infused into the patient after the surgery is 5-15 mg/kg/hour of citrulline.

7. The composition of any one of claims 1-6, wherein the effective amount of citrulline is sufficient to raise a patient's plasma citrulline level above 100 $\mu\text{mol/L}$.
8. The composition of any one of claims 1-7, wherein the effective amount of citrulline is sufficient to raise the patient's plasma citrulline level for up to 48 hours postoperatively.
9. The composition of any one of claims 1-8, wherein the patient is less than about 6 years old.
10. The composition of any one of claims 1-8, wherein the patient is less than about 10 days old.
11. The composition of any one of claims 1-8, wherein the patient is at risk for persistent pulmonary hypertension of the newborn (PPHN).
12. The composition of any one of claims 1-11, wherein the period between the initiation of surgery and the administration of the post-surgery bolus is 4 hours or less.
13. The composition of any one of claims 1-11, wherein the citrulline infusion is started within 5–10 minutes of the post-surgery citrulline bolus.
14. The composition of any one of claims 1-11, wherein the method further comprises a citrulline bolus formulated to be administered prior to the surgery.
15. The composition of any one of claims 1-11, wherein the patient achieves a sustained citrulline level of 100 $\mu\text{mol/L}$ or above for up to 48 hours starting with the administration about 100–300 mg/kg citrulline to the patient at the initiation of the surgery.