Oregon Health & Science University
School of Medicine

Scholarly Projects Final Report

Title *(Must match poster title; include key words in the title to improve electronic search capabilities.)*

Does Renal and Hepatic Function Predict Likelihood of Experiencing Citrate Poisoning in Apheresis?

Student Investigator's Name

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Project Course *(Indicate whether the project was conducted in the Scholarly Projects Curriculum; Physician Scientist Experience; Combined Degree Program [MD/MPH, MD/PhD]; or other course.)*

Scholarly Projects Curriculum

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Mentor's Name

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BME Department

Scholarly Project Final Report

Concentration Lead's Name

Peter Mayinger

Project/Research Question

Does renal and hepatic function predict likelihood of experiencing citrate poisoning in blood transfusion procedures such as apheresis?

Type of Project *(Best description of your project; e.g., research study, quality improvement project, engineering project, etc.)*

Research study.

Key words *(4-10 words describing key aspects of your project)*

Citrate Toxicity, Hypocalcemia, Live function, renal function

Meeting Presentations

If your project was presented at a meeting besides the OHSU Capstone, please provide the meeting(s) name, location, date, and presentation format below (poster vs. podium presentation or other).

Publications *(Abstract, article, other)*

If your project was published, please provide reference(s) below in JAMA style.

N/A

Submission to Archive

Final reports will be archived in a central library to benefit other students and colleagues. Describe any restrictions below (e.g., hold until publication of article on a specific date).

No restrictions.

Scholarly Project Final Report

Next Steps

What are possible next steps that would build upon the results of this project? Could any data or tools resulting from the project have the potential to be used to answer new research questions by future medical students?

Changing the parameters and expanding the sample size.

Student's Signature/Date *(Electronic signatures on this form are acceptable.)*

This report describes work that I conducted in the Scholarly Projects Curriculum or alternative academic program at the OHSU School of Medicine. By typing my signature below, I attest to its authenticity and originality and agree to submit it to the Archive.

X _____

Student's full name

Mentor's Approval *(Signature/date)*

X _____

Mentor Name

Scholarly Project Final Report

Report*: Information in the report should be consistent with the poster, but could include additional material. Insert text in the following sections targeting 1500-3000 words overall; include key figures and tables. Use Calibri 11-point font, single spaced and 1-inch margin; follow JAMA style conventions as detailed in the full instructions.*

Introduction *(≥250 words)*

Two of the most common forms of anticoagulation in apheresis and blood transfusion involves the use of citrate or heparin. Apheresis is a technique that involves drawing out blood from patients, removing excess white blood cells, or plasma, or immunoglobulins, and then returning the filtered blood back into the patient [1]. Anticoagulation during apheresis and blood transfusion prevents blood clots that may lead to ischemia of the heart, brain, kidneys, lungs and many other organs. Both techniques, however, comes with the risk of bleeding as the therapeutic windows are very narrow and hard to achieve due to the multitude of unique comorbidities that patients present with.

Patients with blood disorders such as leukemia, multiple myeloma, polycythemia vera, or any other forms of cancer can benefit from apheresis as it can filter the blood as well as help harvest stem cells for immunotherapy for many different cancers. The risk of citrate related complications in such patient population is 7.8% for plasma exchange and 48% for stem cell harvest [1]. Hypocalcemia is one of the many complications which can lead to symptoms such as headaches, nausea, tremors, hypotension, cramping, and when severe can lead to seizures and cardiac arrhythmias [2].

Although there have been studies looking into the risks, side effects, and potential causes of citrate toxicity, there is not much evidence in screening the risk of individual patients, how much does liver or kidney function affect likelihood or experiencing hypocalcemia due to citrate poisoning. This project will aim to address how we can better manage the therapeutic windows of patients getting citrate and ultimately allow patients to undergo apheresis or blood transfusions safely.

Methods *(≥250 words)*

The patient data was collected retrospectively through chart review in the electronic health records at OHSU's Apheresis Clinic with IRB approval. Patients were identified in the schedule at the Apheresis Clinic undergoing total plasma exchange. Starting in August of 2021, patients were identified via going back each day in the schedule until September of 2020. Patients' age, sex, creatinine, AST, ALT, albumin, and calcium levels were recorded and stored according to IRB protocol. Various apheresis parameters such as flow rate of citrate, calcium, and total amount of their used during the apheresis run was recorded. For patients experiencing complications due to hypocalcemia, their different subjective experiences were recorded from their EHR. Any patient who was less than 18 years old were excluded from this study.

Out of the 100 total apheresis runs recorded, dating back to 2020, the patients experiencing complications were split into a different group than the patients who were symptom free. Patients who reported symptoms were placed in the complications (C) group. Eight apheresis runs were excluded due to either incomplete data or erroneous entry in their electronic health records. Most recent laboratory values before their apheresis were considered the patients' baseline. For patients who required multiple apheresis runs, their individual runs were regarded as a different subject in this study.

The mean and standard deviations of their baseline laboratory values for the two groups' renal and hepatic functions, quantity and rate of citrate and calcium used during apheresis were calculated in Microsoft Excel.

Two sample t-test with alpha of 0.05 was done in Microsoft Excel looking at the significance between the baseline laboratory values and apheresis parameters between the two groups. Confidence intervals were also calculated in Excel.

Results *(≥500 words)*

There was a total of 92 subjects that were included in this study and of those 10 had complications (**Table 1**). Of the 92 subject, 39 were female while 53 were male. The most common symptom of citrate toxicity reported was paresthesia of the mouth and hand (**Table 2**). The other symptoms included nausea, dizziness, headache, vomiting, hives, and chest pain (**Table 2**). The average age of the group with complications (C) and without (N) were 45 and 43 respectively with a p-value of 0.68 (see **Table 1**). Some of the different indications for plasma apheresis included focal segmental glomerulosclerosis, cold autoimmune hemolytic anemia, granulomatosis with polyangiitis, myasthenia gravis, optic neuritis, heart failure, autoimmune encephalitis, thrombotic thrombocytopenic purpura, and rapidly progressive glomerulonephritis. One unanticipated finding during chart review was that laboratory studies of the liver and renal function were not always done the day of plasma apheresis, but rather within the last two weeks. There were a few patients who received multiple apheresis runs, but each were recorded as if they were different subjects in this study. Lastly, plasma apheresis parameters were constantly changing during the entirety of the different runs, thus the parameters recorded were based on the values that were consistent for most of the running time.

Average liver function value of AST was 27 (U/L) and 23 U/L) in the C and N group respectively with p-value of 0.9 (Table 1). Average ALT was 40 (U/L) and 28 (U/L) of the C and N group respectively with p-value of 0.65. Platelets, which served as a proxy for liver's synthetic function was 166 (k/mm^3) and 176 (kmm^3) respectively with p-value of 0.648. Albumin was another proxy for liver's synthetic function between the C and N groups their values were 3.62 (g/dL) and 3.86 (g/dL) respectively with p value of 0.12. The average creatinine, a proxy for kidney's ability to eliminate citrate, was 1.50 (mg/dL) and 1.49 (mg/dL) for the C and N group respectively with p-value of 0.926. Ionized calcium levels prior to start of plasma apheresis was 1.17 and 1.22 in the C and N group respectively with p-value of .121. Serum calcium before apheresis was 9.12 and 9.44 for C and N group respectively with p-value of 0.189. Subject's serum pH was also recorded but not included in the tables below and they were 7.37 for the C group and 7.36 for the N group with p-value of 0.9.

The average total apheresis time for the C and N groups were 114 minutes and 106 minutes respectively with p-value of 0.439. The average amount of citrate used between the C and N groups were 122 ml and 100 ml respectively with p-value of 0.188. Rate of calcium replacement in the form of calcium gluconate were 89 (ml/hr) in the C group compared to 71 (ml/hr) in the N group with p-value of 0.010. Total calcium replaced was 167 mL and 134 mL with p-value of 0.093. The citrate infusion rate was 1.08 (mL/min) and 1.16 (mL/min) with p-value of 0.494.

Table 1: Baseline renal and liver functions and apheresis parameters

Baseline demographics, liver, renal functions, and apheresis parameters	With Complications (C)	No Complications (N)	p-Value (two tail)
Number of Subjects (N)	10	82	
Age	45 ± 11	43 ± 3	0.68
AST (U/L)	27 ± 9.7	23 ± 6.1	0.9
ALT (U/L)	40 ± 20.9	28 ± 6.3	0.65
Platelet (K/mm^3)	166 ± 49.2	176 ± 19.2	0.648
Creatinine (mg/ dL)	1.50 ± 0.86	1.49 ± .26	0.926

Albumin (g/ dL)	3.62 ± 0.4	3.86 ± .10	0.139
Ionized calcium before apheresis (mmol/L)	1.17 ± .08	1.22 ± .02	0.121
Serum Calcium level (mg/ dL)	9.12 ± .51	9.44 ± .15	0.189
Total citrate (mL)	122 ± 63	100 ± 8	0.188
Calcium Gluconate Rate (mL/hr)	89 ± 14	71 ± 4	0.010
Total Calcium replaced (mL)	167 ± 36.8	134 ± 11.7	0.093
Total citrate/Apheresis time (mL/ min)	1.08 ± .40	1.16 ± 7.93	0.494
Calcium replaced/Apheresis time (mL/ min)	1.51 ± .20	1.26 ± 0.7	0.030
Total Apheresis Time (min)	114 ± 28	106 ± 6	0.439

Table 2: Reported symptoms experienced in the subjects with complications (C)

Complications (symptoms experienced)
Paresthesia of tongue and mouth
Paresthesia of mouth
Nausea
Dizziness and Headache
Paresthesia
Paresthesia
Vomiting
Mild tinging of left hand
Rash of body and face
Hives, pruritis, and chest pain

Discussion *(≥500 words)*

The baseline liver and renal function laboratory values between the C and N groups were not significantly different based on the p-values above the alpha of 0.05. The albumin which binds to citrate along with calcium levels before plasma apheresis was insignificantly different as well, suggesting that the risk factors for citrate toxicity in the setting of using citrate as an anticoagulant in apheresis is more complex [3]. It was interesting to note the significant difference of the calcium gluconate rate as well as the average calcium replacement rate (p= 0.01 and p= 0.03 respectively) were higher in the group with complications. Factors such as age and gender were not a significant factor in this study (p= 0.68) to explain why some of the subjects experienced symptoms of citrate toxicity. Most of the symptoms experienced were consistent with hypocalcemia [4] because it has been known that citrate in excess would bind to cations such as calcium leading to decreased ionized calcium levels [1].

It is known that citrate is both metabolized through the Kreb's Cycle in the mitochondria and that approximately 20% of unmetabolized citrate is excreted by the kidneys [2] [5]. The idea behind this study was that if either the renal or liver functions were impaired, then patient would be at an increased risk for developing citrate toxicity, but this study did not show a significant relationship with either the kidney or liver functions in laboratory findings. It is difficult to assess the degree of impairment before the respective organs' ability to excrete or metabolize citrate is affected. The laboratory results, however only measure a small fraction of the vast function of the liver and kidneys. Different patients have different comorbidities, the vast range of normal laboratory values, and unknown underlying liver and renal pathologies not

accounted for in this study could have showed a clearer relationship of renal and liver function with citrate toxicity. Additionally, plasma apheresis is protocolized at the OHSU Apheresis Clinic such that any abnormal ionized calcium levels measured during apheresis or symptoms prompted increased calcium replacement to reverse possible complications of hypocalcemia. The protocol was shown through the significance in the amount of calcium used in the C group (see Table 1). Thus, this further mask any relationships this study aimed to address. As a retrospective study it was difficult to acquire a consistent set of data to compare, such as same day liver and renal functions prior to apheresis, unaccounted for liver or renal pathologies, and the accuracy of the documentation in the EHR by staff members supporting the subjects undergoing plasma apheresis.

The sample size of (N=10) the subjects with complications was small and thus less power for this study to detect significant differences between the two populations. Patients had multiple plasma apheresis over time and thus accounting them as different subjects may have homogenized the two groups and thus making it difficult to reject the null hypothesis that the two groups are the same. Currently the results from this study does not change clinical practice in plasma apheresis. However, future studies with a more holistic approach to assessing renal and liver functions and only studying patients once instead of counting their multiple plasma apheresis runs as different subjects and increasing the sample size for subjects with complications could better elucidate the relationship of interest.

Conclusions *(2-3 summary sentences)*

This study did not show the relationship theorized between citrate toxicity with renal or liver impairments. However, future studies addressing the limitations of limited data in a retrospective study and increasing the sample size could support an underlying relationship. That relationship will be instrumental in dictating a safer clinical practice where citrate is used, especially in patients with underlying renal or hepatic impairments.

References *(JAMA style format)*

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2. Ludbrook, J. and V. Wynn, *Citrate intoxication; a clinical and experimental study.* British medical journal, 1958. **2**(5095): p. 523-528.
3. Toffaletti, J., et al., *Influence of Continuous Infusion of Citrate on Responses of Immunoreactive Parathyroid Hormone, Calcium and Magnesium Components, and Other Electrolytes in Normal Adults during Plateletapheresis*.* The Journal of Clinical Endocrinology & Metabolism, 1985. **60**(5): p. 874-879.
4. Wirguin, I., et al., *Citrate-Induced impairment of neuromuscular transmission in human and experimental autoimmune myasthenia gravis.* Annals of Neurology, 1990. **27**(3): p. 328-330.
5. Farrokhi, P., et al., *How to Stabilize the Level of Ionized Calcium and Citrate during Plateletpheresis.* 1998. **74**(1): p. 7-12.