

**INTERCHANGEABILITY OF THE I-STAT POINT OF CARE ANALYZER WITH CENTRAL
LABORATORY TESTING IN AN EMERGENCY DEPARTMENT SETTING**

A Thesis submitted to the University of Arizona College of Medicine -- Phoenix
in partial fulfillment of the requirements for the Degree of Doctor of Medicine

Colin Little
Class of 2015

John Sarko, MD

Acknowledgments

I would like to take this opportunity to thank my mentor, Dr. John Sarko. Dr. Sarko was invaluable to me in completing this project, but above and beyond that, he was always willing to give advice on life and career. He was also exceeding active at my school, touching almost every person who passed through, always in subtle but positive ways. The sum total of his impact on us is immense. He was a wonderful human being and served as an inspiration to hundreds of people, myself included. We will miss him.

Table of Contents

Introduction	1
Materials and Methods	2
Results	3
Potassium	3
Sodium	8
Bicarbonate	11
Chloride	15
Discussion	19
Future Directions	19
Conclusions	20

Figure 1: Potassium - 60 Minute Timeframe	5
Figure 2: Potassium - 15 Minute Timeframe	7
Figure 3: Sodium - 60 Minute Timeframe	9
Figure 4: Sodium - 15 Minute Timeframe	10
Figure 5: Bicarbonate - 60 Minute Timeframe	12
Figure 6: Bicarbonate - 15 Minute Timeframe	14
Figure 7: Chloride - 60 Minute Timeframe	16
Figure 8: Chloride - 15 Minute Timeframe	18

Abstract

Background and Significance:

The i-STAT point of care blood analyzer is a handheld device used for a variety of laboratory analyses in medical settings. Much research has been performed to evaluate its validity, but it has not been exhaustively tested in real-world emergency department settings, despite its increasingly popular use in such settings.

Methods:

We retrospectively examined medical records at the Maricopa Integrated Health Systems Emergency Department to find 100 instances between February 2014 and September 2014 in which a patient had electrolyte testing performed on both the i-STAT and in the central laboratory within a 60 minute timeframe. These data were examined using variance of means and Bland-Altman graphing for equivalency.

Results:

We set the clinical equivalence threshold for each lab to be 5% of the mean normal value. That is, if the i-STAT differed from central lab by less than 5% of the middle of the normal range (137-145 for sodium, 5% of which is 7) then we consider them to be clinically equivalent. At this level we were unable to show clinical equivalence. In addition, all electrolytes tested showed small but significant bias between the i-STAT and the central laboratory. Re-examination of the data excluding all measurements more than 15 minutes apart showed similar findings.

Conclusions:

At this time we cannot show equivalency between the i-STAT device and the central laboratory when used under real-life emergency department conditions. More research is needed to support or refute these findings.

Introduction

Point of care testing (POCT) blood analyzers such as the i-STAT system manufactured by Abbott Laboratories have become increasingly common in emergency department settings. These devices allow common blood tests to be performed at the bedside instead of in the central hospital laboratory, and therefore have the potential to improve efficiency, improve patient outcomes, and perhaps reduce costs¹. These devices have been available for more than two decades, with the first published, independent analysis performed in 1993². One of the most popular uses for the i-STAT and other POCT systems is to test for clotting time, and there is substantial literature available showing that these devices are sufficiently equivalent to central laboratory testing³⁻⁷. Similarly exhausting testing has not been performed for other critical measures that would be necessary for widespread use in the emergency department setting.

We evaluated the i-STAT POCT system for use in testing sodium, potassium, creatinine, bicarbonate, and chloride. Creatinine, potassium, and bicarbonate have been evaluated previously and found to be interchangeable with central laboratory testing, but they have not been studied extensively in an emergency department setting^{1, 8, 9}. In addition, much of the testing that has been done on these POCT systems has isolated the test itself and not evaluated its use in a broader context. Often specific samples are drawn for use in the test by trained laboratory personnel who are aware their samples will be used for research purposes. We attempted to eliminate this potential source of bias by comparing results from samples drawn during patient visits to the emergency department

Our hypothesis was that the i-STAT systems are interchangeable with central laboratory testing for sodium, creatinine, potassium, bicarbonate, and chloride in emergency department settings. We defined interchangeable as having 95% of their lab differences less than our clinical equivalency threshold, which we set to be 5% of the mean normal lab value. Support for this hypothesis would validate the use of these devices in the emergency department, with the associated increase in efficiency and reduction in patient wait times, and add to the existing literature.

Materials and Methods

An EPIC chart review of all adult patients seen at the Emergency Department at Maricopa Integrated Healthcare Systems Medical Center was performed to identify all patients between February 2014 and September 2014 who had sodium, potassium, chloride, or bicarbonate testing performed using the i-STAT POCT system. These patients were then checked for a central lab result within 60 minutes of the i-STAT result that could be used for comparison. We had hypothesized that 100 patients would be sufficient for data analysis as there is no sample size calculation for Bland-Altman comparisons. 100 consecutive patients were identified. These patients were had their identifying information abstracted and their lab data collected for analysis. Hemolyzed samples were not included.

Equivalency tests were performed using Bland-Altman plots through gnuplot. All statistical analysis was performed using the R statistical package. Bland-Altman plots are a standard method for visualizing if two clinical tests are equivalent. The plot presents the average of the i-STAT and central lab on the x-axis and the difference between those two on the y-axis. By plotting each of our lab values on these axes it is possible to see if the results cluster near the 0 point on the y-axis, which would represent no difference between the i-STAT and central lab. It is also possible to see if there is more significant difference between i-STAT and central lab at specific points along the x-axis, which represents the range of possible lab values. Overall, these plots allow a quick visualization of how equivalent the two tests are.

It is also possible to make quantitative conclusions using these graphs. For this analysis, we set a clinical threshold of equivalency and see if 95% of the lab values have a difference between i-STAT and central lab that falls within that threshold. If that is true, then we can claim equivalence between the two tests. On the plots that follow, the clinical equivalency threshold is represented by the blue dashed line. The black dashed lines represent the 95% confidence intervals for the difference between the i-STAT and central lab. For the two tests to be equivalent the black dashed lines would have to be contained within the blue dashed lines.

To use these plots properly, it is essential to properly set the threshold of clinical significance. This is inherently a judgment call as there is no quantitative way to perform this task. For this study, the threshold of clinical significance was set at 5% of the mean “normal”

value for a given lab. For example, sodium has a normal range of 135 to 147 at the Maricopa Medical Center Emergency Department's central lab. We therefore set the threshold of clinical significance to 7, which is 5% of 141, the midpoint of the normal range. The i-STAT POCT was declared to be equivalent to central laboratory testing if the 95% confidence interval (1.96 SD) was contained entirely within the threshold of clinical significance for a given test.

Bias was also examined using Bland-Altman plots. Bias is the overall difference between the i-STAT and central lab. This is represented on the graph by a central black dashed line, and also by the red line showing the regression analysis. If the average difference between i-STAT and central lab is 0, then there is no bias. If it is positive, then the i-STAT routinely overestimates the lab value. Likewise, if it is negative the i-STAT is routinely underestimating the actual lab value. If the regression curve is not flat, then the bias changes depending on where the value falls along the range of possible values.

Results

Results are presented for both a 60 minute maximum interval between the i-STAT and central lab testing and for a 15 minute timeframe. We have 100 patients for the 60 minute timeframe and 71 for the reduced timeframe of 15 minutes. There are four laboratory tests that we studied: potassium, sodium, bicarbonate, and chloride. None of these shows equivalence, and all show small but significant bias.

Potassium

The mean normal potassium value is 4.3 (range of 3.5 to 5.1), which gives a clinical equivalency threshold of 0.215. As shown below in Figure 1, the 95% CI runs from -1.49 to 0.86, which is significantly outside the threshold on both endpoints. Furthermore, there is a significant negative bias of -0.31, which indicates that the i-STAT device routinely underreports the true potassium level. Perhaps most interestingly, the i-STAT appears to be much more accurate at potassium levels below 5. Above this level the bias appears to increase with several data points showing i-STAT overestimations of 1 to 2.5. In addition, the regression curve (shown as the red line) makes a significant increase at that point, although the 95% confidence

interval shown (shown as the shaded grey) does increase showing increased uncertainty at that level.

Potassium - 60 Minute Timeframe

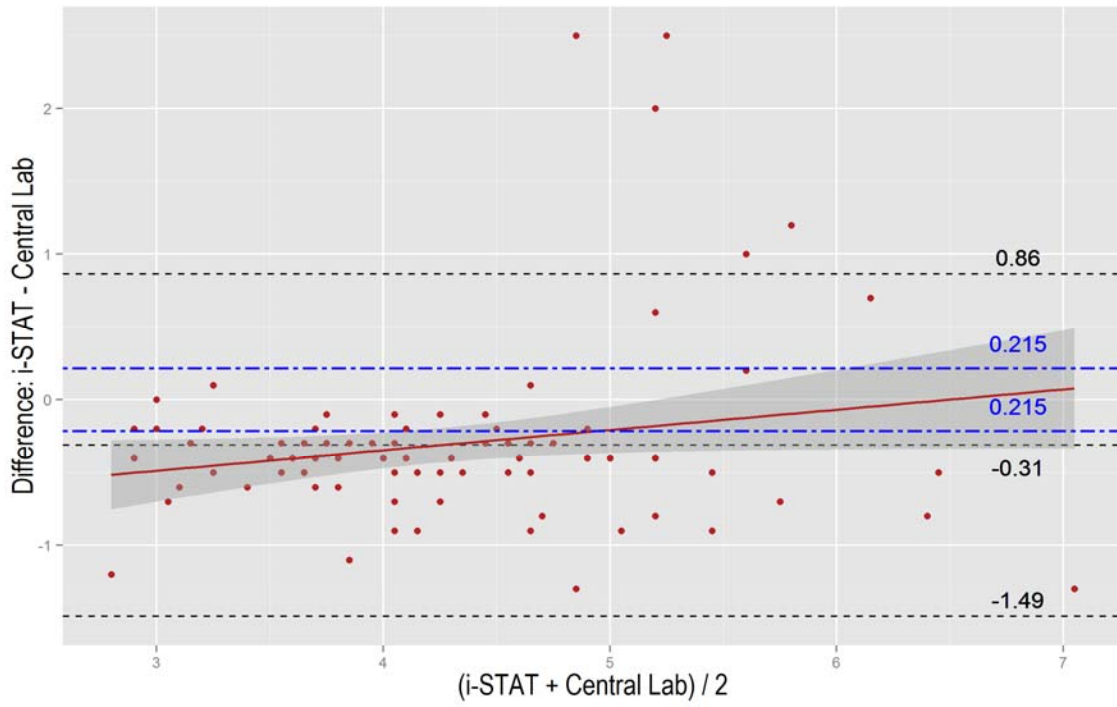


Figure 1: Potassium - 60 Minute Timeframe

Lowering the allowable time difference between the two lab tests from one hour to fifteen minutes did not appreciably alter the results, as shown in Figure 2. The overall bias remains similar at -0.39 and the 95% confidence interval of the difference between the i-STAT and central lab is significantly outside our threshold of clinical significance with the 95% confidence interval covering a difference of -1.3 to 0.53.

Potassium - 15 Minute Timeframe

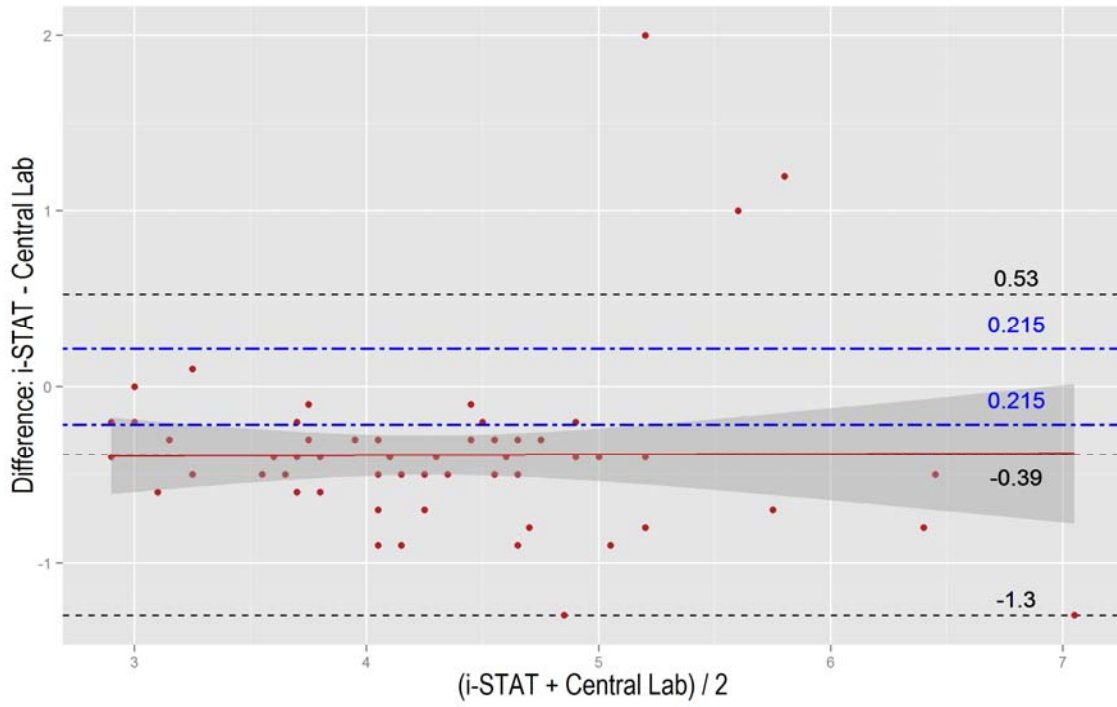


Figure 2: Potassium - 15 Minute Timeframe

Sodium

The threshold of clinical significance for sodium is 7, which we set by taking 5% of the mean normal value of 141. This lab comes closest to clinical significance, but does not meet the threshold as the 95% confidence interval of -8.99 to 2.33 exceeds the threshold on the negative end. The overall bias shows that the i-STAT routinely underestimates sodium by only 3.33, a value which is consistent over the range of values as shown by the regression curve in red. Qualitatively, it appears that most of the underestimation performed by the i-STAT is in the normal range, which would suggest that it may be at values which are less clinically important.

Reducing the maximum allowable timeframe between the i-STAT and central lab testing again had no significant impact on the results. As shown in Figure 4, the 95% confidence interval of lab values is essentially unchanged at -8.99 to 2.24. The mean bias is also essentially the same at -3.38.

Sodium - 60 Minute Timeframe

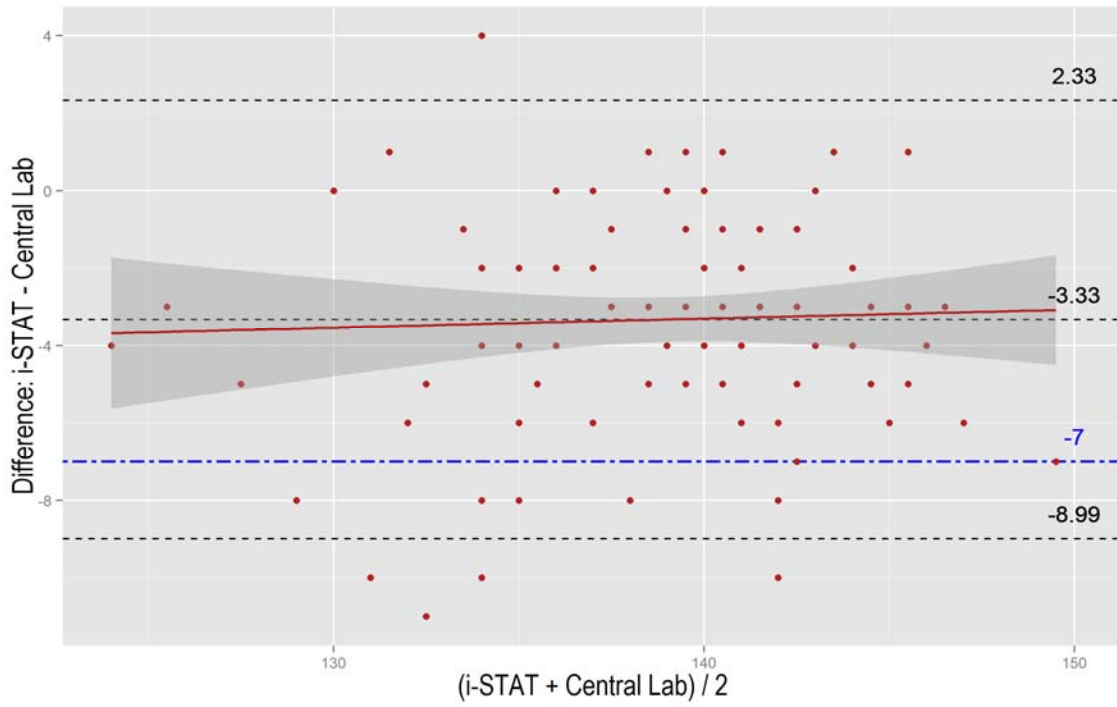


Figure 3: Sodium - 60 Minute Timeframe

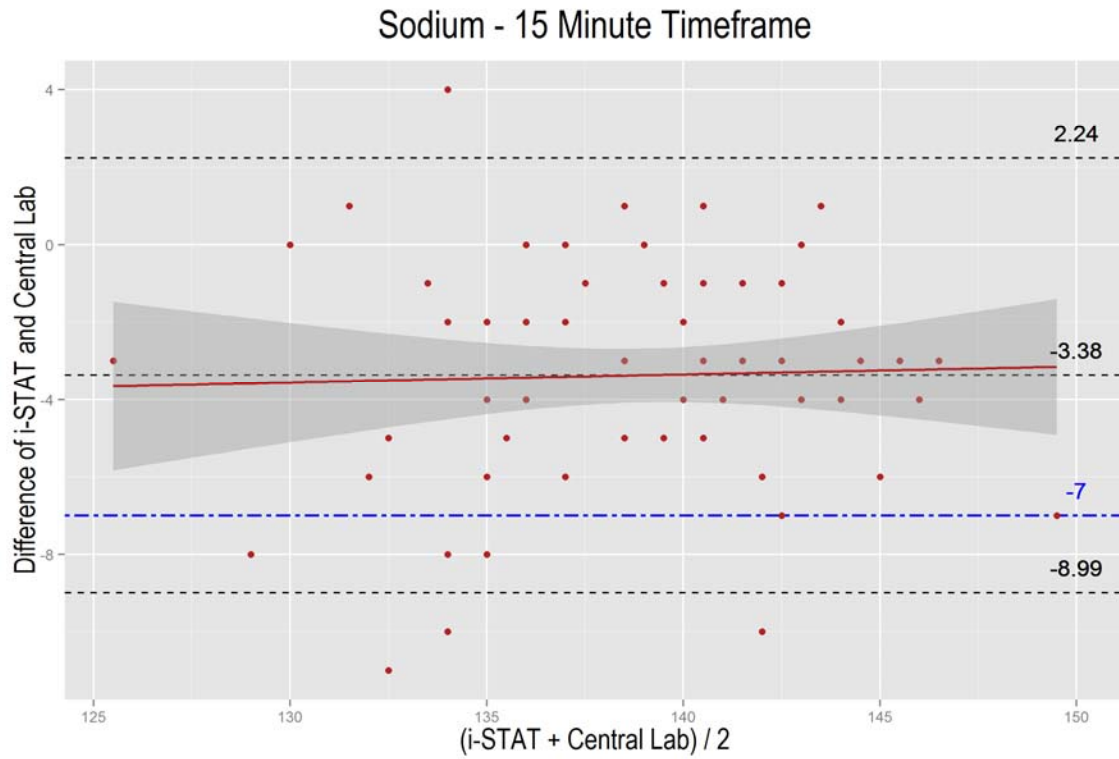


Figure 4: Sodium - 15 Minute Timeframe

Bicarbonate

Similarly for bicarbonate, the 95% CI of mean difference falls outside our threshold of clinical significant. The mean normal bicarbonate value is 26, which gives a threshold of 1.3. As seen in Figure 5, the 95% confidence interval runs from -5.75 to 4.78, which is significantly outside the threshold. Therefore, we cannot claim equivalence between the i-STAT and central lab testing. A small negative bias exists at -0.49 showing that i-STAT routinely underestimates bicarbonate. No obvious correlation exists between the lab value and mean difference.

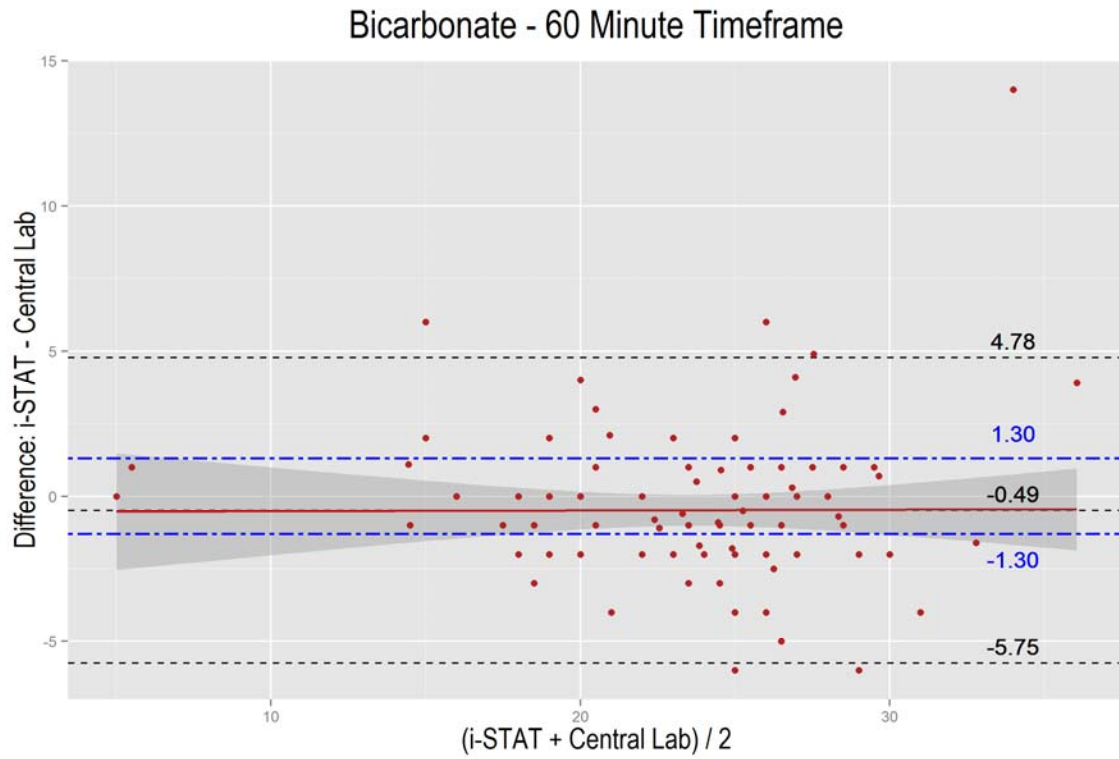


Figure 5: Bicarbonate - 60 Minute Timeframe

As on the other lab tests, decreasing the maximum allowable timeframe between the i-STAT test and the central lab doesn't significantly alter the results. As shown in Figure 6, the 95% confidence interval of -4.62 to 3.57 is significantly outside our threshold of clinical significance. The bias is basically unchanged at -0.52, and although the regression curve does show a difference in bias throughout the range of values, that appears to be overly influenced by a single outlier at the low end of the range. The 95% confidence interval on the regression curve (shown by the grey region) includes a flat line, which indicates that we cannot claim and correlation between mean difference and lab value.

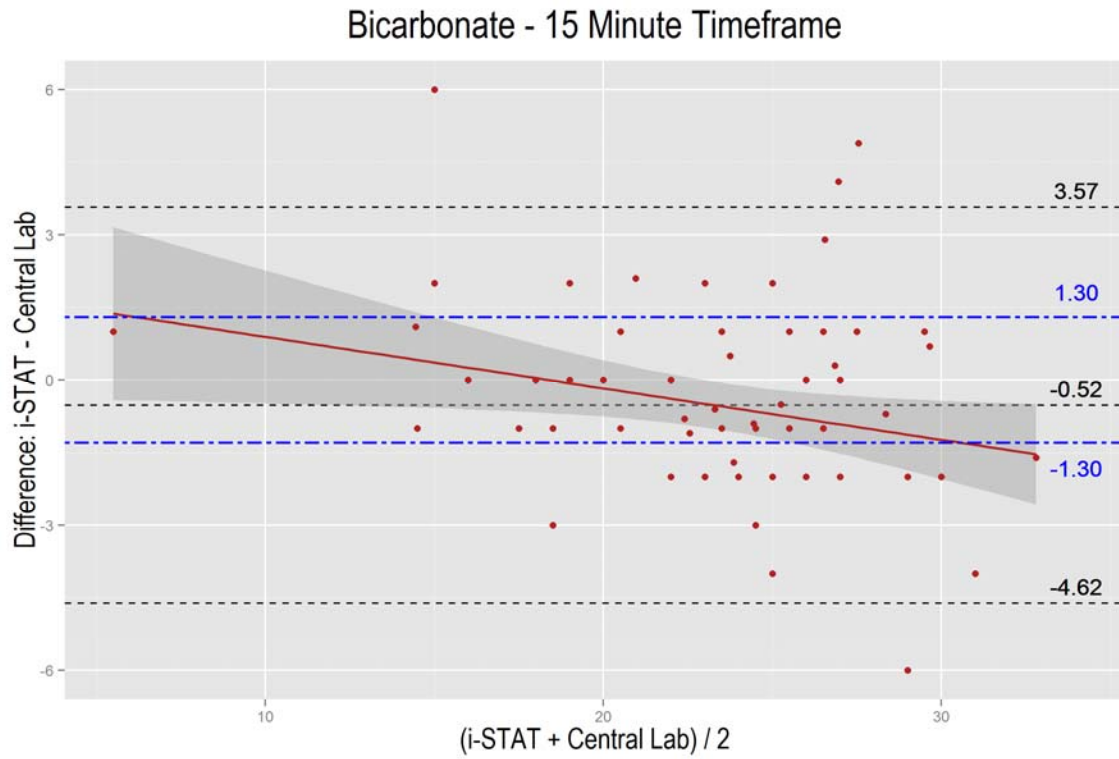


Figure 6: Bicarbonate - 15 Minute Timeframe

Chloride

The midpoint of the normal value for chloride is 103, and therefore we set the threshold of clinical significance at 5.2. As shown in Figure 7, the 95% CI for mean difference is -6.24 to 8.1, which falls outside the threshold on both positive and negative endpoints. Therefore, we cannot claim equivalency for this lab. The mean bias is 0.93, indicating that the i-STAT routinely overestimates chloride by a small measure. A slight negative correlation is also present, although the 95% confidence interval (shown as the dark grey region) shows that this correlation is not statistically significant.

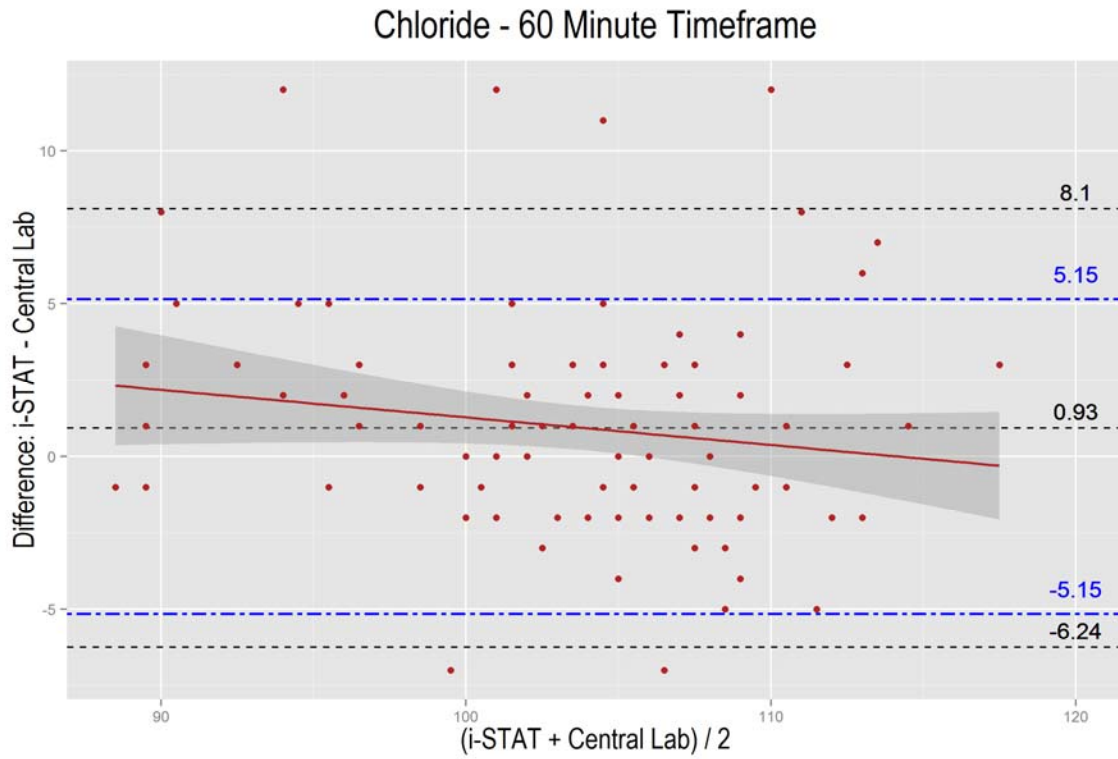


Figure 7: Chloride - 60 Minute Timeframe

Much like the other lab tests in this study, reducing the maximum allowable time interval between the two labs to 15 minutes from one hour does not significantly alter the results. As shown in Figure 8, the 95% confidence interval of -5.84 to 8.76 is still outside the threshold of clinical significance. The bias remains above zero at 1.46, indicating that the i-STAT is reporting slightly higher values than the central lab. Again, a slight negative correlation is present, but is not statistically significant.

Chloride - 15 Minute Timeframe

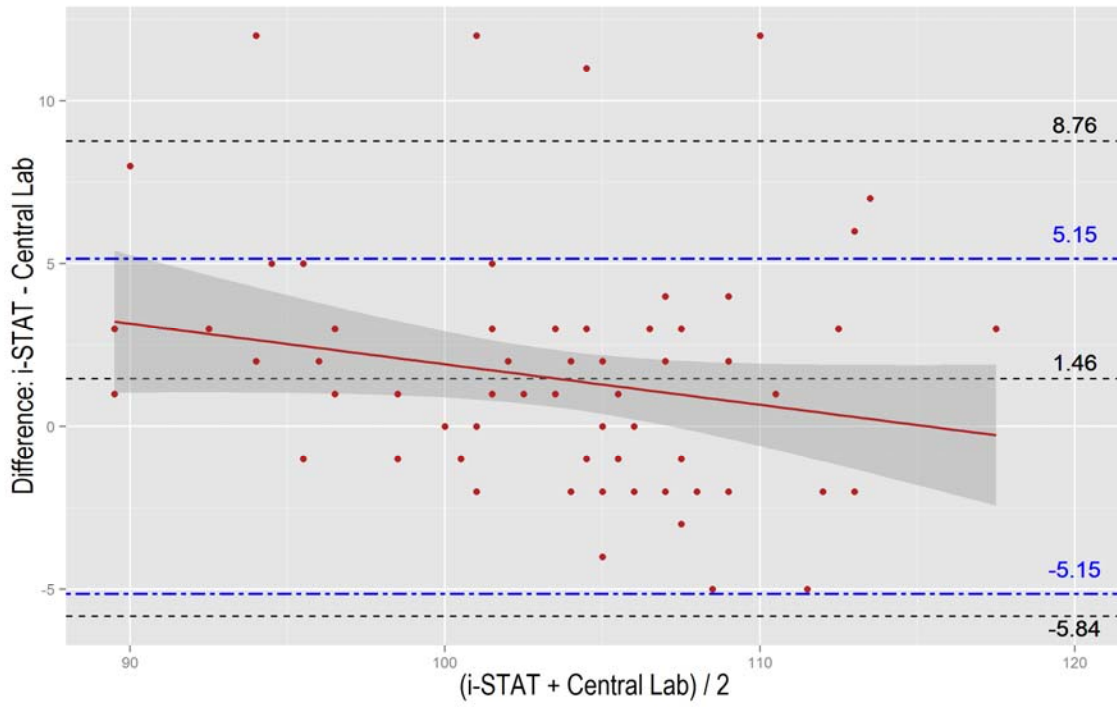


Figure 8: Chloride - 15 Minute Timeframe

Discussion

All of our 95% CI ranges exceed the threshold of clinical significance on at least one end of their range, with most exceeding both endpoints. Therefore, there is no test on which we can claim equivalence between central lab testing and the i-STAT POCT system. All of the tests had small but significant bias in which the i-STAT either routinely overestimated or underestimated the lab value.

One potential criticism is that we initially allowed for 60 minutes between the two different testing modalities. During that time, the patient may have received treatment which would have altered their labs, which would create artificial variance between the two lab results. Or, it is possible that the patient's underlying medical condition caused this value to change without medical intervention. To examine this potential, we ran the data using only instances in which the two lab results were drawn within 15 minutes of each other. This reduced our sample size from 100 to 71, and as shown in the results section, there was no significant difference in the results.

Another point of discussion is the selection of our threshold of clinical significance. This is inherently subjective. Because we are looking at a range of values for each lab, we decided to implement a standardized threshold of 5% of the mean normal value across the range. This allows for some variance between the two methodologies but constrains the variance to levels that most clinicians would interpret as not clinically relevant. It is important to note that for potassium and bicarbonate the 95% confidence interval of the difference between the i-STAT and the central lab greatly exceeded the threshold. Even had we set the threshold at 15% of the mean normal value we still would not have been able to show clinical equivalence. For sodium and chloride the difference was less, but still significantly outside our threshold.

Future Directions

Additional study with greater sample size would be useful to definitively show non-equivalence. It would also be beneficial to repeat this study as a prospective trial with both the i-STAT and central lab testing performed on the same blood draw at the same time. This would

eliminate the potential for variance over time which may have artificially increased the error in our study, even with a 15 minute window.

Another potential improvement would be to use a relative threshold of clinical significance rather than the fixed value that was used in this study. By looking for a difference of less than 5% across all ranges, rather than 5% of the mean normal value, we would allow for increased variance at the higher ranges, which may be less clinically significant. It would also require less variance at the lower lab values, where a smaller difference may be more clinically relevant. Another potential form of analysis which could be utilized would be to categorize the data into critically low, low, normal, high, and critically high and consider a difference to be clinically significant only if it causes a lab value to move from one category to the other. This would be most useful for determining if the i-STAT could be used as a screening tool, such as for hypo/hyperkalemia. As shown in this study, the i-STAT is unreliable at high potassium levels, so treatment would require central laboratory testing to determine the exact value of the hyperkalemia.

Conclusions

The i-STAT POCT testing system is a quick and efficient tool for rapid assessment of electrolytes in the emergency department. However, we were unable to show that it is equivalent to central laboratory testing for sodium, potassium, chloride, or bicarbonate with a threshold of clinical significance of 5% of the mean normal value for each lab. The results show small but significant bias on each lab result, and appear to be particularly unreliable for potassium values over 5. As this tool is primarily used as a screening test to determine if additional testing is needed, the significant variance at high levels of potassium, and the smaller, but still significant variance in sodium, chloride and bicarbonate levels indicate that without additional study showing equivalence the i-STAT POCT system should not be used in isolation for clinically important decision making.

REFERENCES

1. Lee-Lewandrowski E, Chang C, Gregory K, Lewandrowski K. Evaluation of rapid point-of-care creatinine testing in the radiology service of a large academic medical center: Impact on clinical operations and patient disposition. *Clin Chim Acta*. 2012;413(1-2):88-92.
2. Erickson KA, Wilding P. Evaluation of a novel point-of-care system, the i-STAT portable clinical analyzer. *Clin Chem*. 1993;39(2):283-287.
3. Karon BS, McBane RD, Chaudhry R, Beyer LK, Santrach PJ. Accuracy of capillary whole blood international normalized ratio on the CoaguChek S, CoaguChek XS, and i-STAT 1 point-of-care analyzers. *Am J Clin Pathol*. 2008;130(1):88-92.
4. Boehlen F, Reber G, de Moerloose P. Agreement of a new whole-blood PT/INR test using capillary samples with plasma INR determinations. *Thromb Res*. 2005;115(1-2):131-134.
5. Lewandrowski EL, Van Cott EM, Gregory K, Jang IK, Lewandrowski KB. Clinical evaluation of the i-STAT kaolin activated clotting time (ACT) test in different clinical settings in a large academic urban medical center: Comparison with the medtronic ACT plus. *Am J Clin Pathol*. 2011;135(5):741-748.
6. Karon BS, Scott R, Burritt MF, Santrach PJ. Comparison of lactate values between point-of-care and central laboratory analyzers. *Am J Clin Pathol*. 2007;128(1):168-171.

7. Spielmann N, Mauch JY, Madjdpour C, et al. Comparison of point-of-care testing (POCT): I-STAT((R)) international normalized ratio (INR) vs reference laboratory INR in pediatric patients undergoing major surgery. *Paediatr Anaesth*. 2011;21(10):1041-1045.

8. Leino A, Kurvinen K. Interchangeability of blood gas, electrolyte and metabolite results measured with point-of-care, blood gas and core laboratory analyzers. *Clin Chem Lab Med*. 2011;49(7):1187-1191.

9. Thomas FO, Hoffman TL, Handrahan DL, Crapo RO, Snow G. The measure of treatment agreement between portable and laboratory blood gas measurements in guiding protocol-driven ventilator management. *J Trauma*. 2009;67(2):303-13; discussion 313-4.