Calculating Evidence Based Renal Replacement Therapy

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Summary

Transcribing the theoretical aspect of continuous renal replacement therapy (CRRT) to the bedside and delivering a given dose can be difficult. Our aim was to design an excel calculator which would personalise patient's treatment, deliver an effective, evidence based dose of RRT without large variations in practice and prolong filter life. Our calculator prescribes a haemodialfiltration dose of 25ml.kg^{-1}.hr^{-1} whilst limiting the filtration fraction to 15%. We compared the data from a historical group to a calculator group. The median delivered dose reduced from 41.0 ml.kg^{-1}.hr^{-1} to 26.8 ml.kg^{-1}.hr^{-1} with reduced variability that was significantly closer to the aim of 25 ml.kg^{-1}.hr^{-1} ($p<0.0001$). The median treatment time increased from 8.5hr to 22.2hr ($p=0.00001$). Our calculator significantly reduces variation in prescriptions of CVVHDF and provides an evidence-based dose. It is easy to use and provides personal care for patients whilst optimizing CVVHDF delivery and treatment times.

Introduction

The practice of continuous renal replacement therapy (CRRT) has received much scrutiny recently. Issues such as the timing of initiation [1], timing of termination [1,2], type of therapy [3] and dose of therapy [3,4,5], have received considerable attention. The need to write a daily prescription for patients who require CRRT is considered a marker of good clinical practice [6] and there is now good evidence for an optimal dose of renal replacement therapy. [5] In reality, transcribing the theoretical aspects of CRRT to the bedside and delivering a given 'dose' can be difficult. There is a higher turnover of junior medical staff and the complexity of the machinery increases the chances of error.

Our unit is a 24 bedded critical care providing Level 2 and 3 care. In 2011 we had admitted 1326 patients. RRT was received by 157 individuals, resulting in 768 RRT days. We deliver continuous veno-venous haemodiafiltration (CVVHDF) using the Prismaflex (Gambro Ltd) machine. An audit revealed a huge variation in treatment regimes and that many of our CVVHDF circuits prematurely failed, usually well before the maximum 72 hours recommended by the manufacturer. Changes in prescription, in particular alterations in blood flow rates are a recognized cause. [7,8] This was costly and represented a failure to deliver adequate renal support due to the prolonged filter downtimes, a phenomenon that has been also been recognized [9]. A number of problems were identified. Our protocol was to prescribe high blood flow rates on initiation, up to 300ml.min^{-1}. If the circuit access pressure exceeded -100mmHg or the return pressure exceeded +100mmHg then the blood flow rate was reduced so as not to exceed these limits. We had observed that early circuit failure occurred when blood flow through the indwelling vascular catheter was suboptimal due to kinking, hypovolaemia or

inadequate anticoagulation. Our protocol directed the nursing staff to achieve as high a blood flow rate as possible and compounded this problem.

The medical staff wished to see evidence based dosing of RRT. The literature now points to optimal effluent flow rates of 25ml.kg^{-1}.hr^{-1} although higher rates were the norm prior to the publication of the RENAL study. [4,5] However in our practice, this was not translating into consistent prescribing of ultrafiltrate and dialysate flow rates or an appropriate blood flow rate to support these goals. Our aim was to design an excel calculator which would personalise patient's treatment, deliver an effective, evidence based dose of RRT without large variations in practice and prolong filter life.

Method

The Yorkshire and The Humber Leeds East ethics committee granted ethical approval after proportionate review (ref 14/YH/1004). Patient consent was not required.

A calculator had been designed in 2005 by Ricci et al as a way of retrospectively auditing the delivered dose of RRT within their unit [10]. This used calculations that had been validated in a previous study by [11]. We developed this further. The first premise was that the 'dose' of CVVHDF should be 25ml.kg^{-1}.hr^{-1}. The second was that ultrafiltrate, dialysate and blood flow rates were appropriately matched, and that the filtration fraction did not exceed 15%. The third was a blood flow checker. It is unnecessary to run blood flows as high as 300ml.min^{-1} for most patients. However, if blood flow rates are set too low, then clotting within the circuit is likely to occur. We estimated that a blood flow rate of 160 ml.min^{-1} should be adequate for most patients. The fluid solutions were standard lactate based solutions. If the patient was hyperkalaemic, a potassium free solution was used for the replacement and dialysate. We converted to such a bag when the serum potassium was >5.5mmol.L^{-1}. The clinician precribed the hourly fluid loss.

We recruited all patients that had CVVHDF who were aged 18 and over. We excluded patients that required CVVHDF for less than 24hours and who required CVVHDF for fluid removal only. The historical controls were all patients receiving CVVHDF between January 2012 and June 2012 (six months). The data was collected from the inbuilt Prismaflex (Gambro) data card. Additional patient details were then taken from the hospital computer system (when available). Epidemiological data was collected for the patients: age, sex, patient weights, APACHE2 and ICNARC scores.

In the prospective calculator group, the research team was informed when the clinical team decided to start CVVHDF. The clinical team used the calculator to prescribe the CVVDHF. Data regarding the therapy session was collected from a clean electronic data card within the Prismaflex machine as well as a manual recording form completed by the nursing staff attending the patient.

The primary hypothesis was that the calculator would provide an average hourly CVVHDF dose of 25ml.kg^{-1}.hr^{-1} with a reduction in the variation of practice. The secondary endpoints were an increase in the treatment time of each filter set and a change in the total volume of effluent fluid used. The prospective study would also examine the type and number of changes made to the prescribed regime.

The power was determined using the Monte Carlo method of calculating probability distribution. Our previous audit data had 71 filter episodes from 45 patients with a wide variability in data. Assuming the calculator delivered 25-30ml.kg^{-1}.hr^{-1}, then a sample of just 5 filter episodes would be adequate to show a reduction in variability. However a sample size of 30 filter episodes would ensure that we accurately represented the intervention population. Normally distributed data is presented as mean (standard deviation), non-normal data as median (interquartile range). The difference in variation of the effluent flow rates is measured by the Monte Carlo method for non-normal data. Differences in treatment times and total effluent are calculated with the Mann-Whitney U test.

Results

The historical data was collected from the electronic CVVHDF machine log between January 2012 and June 2012. The individual patient details entered into the machine at that time were not sufficient to provide an adequate summary of the historical group's demographic data. The calculator group's data was complete and was collected between December 2013 and May 2014, after the calculator was introduced. The demographic data is displayed in Table 1.

The patients in the calculator group had a lower median flow rate of 26.8ml.kg^{-1}.hr^{-1} (IQR 25.2-29.0) compared to the historical group that had a median flow rate of 41.0ml.kg^{-1}.hr^{-1} (IQR 29.0-89.0) (Table 2). Since the historical effluent rates were significantly non-normal, we performed a Monte Carlo test using bootstrapping from both empirical distributions. The p-value <0.0001 shows that the prospective effluent rates were significantly closer to the optimum of 25ml.kg^{-1}.hr^{-1} compared with the historical effluent rates. The effluent flow rates are compared in the boxplots in Figure 1.

Figure 1. Box plots show the median, interquartile range and outlying flow rates before and after the introduction of the calculator. The flow rates after the calculator was introduced were significantly closer to 25ml.kg^{-1}.hr^{-1} than those before the calculator with less variability ($p<0.0001$).

The treatment times were significantly longer in the calculator group. The median (IQR) was 22.2hr (16.5-44.6) as compared to 8.5hr (2.8-23.0). Mann-Whitney U test for non-parametric data showed $p<0.00001$ (Figure 2). Before the calculator was introduced there were nine (12%) treatments that lasted less than one hour compared to zero after the introduction of the calculator. As a result the total effluent increased from 29.9L (8.6-111.0) to 60.0L (32.1-119.4), $p=0.003$ (Figure 3). See Table 2.

Figure 2. Box plots show the median, interquartile range and outlying treatment times before and after the introduction of the calculator. The treatment times after the calculator was introduced were significantly longer than those before the calculator ($p<0.00001$).

Figure 3. Box plots show the median, interquartile range and outlying total effluent volumes before and after the introduction of the calculator. The total effluent volumes after the calculator was introduced were significantly larger than those before the calculator ($p<0.0003$).

In the calculator group it was recorded if changes had been made to the settings on the CVVHDF machine (Table 3). The most commonly changed parameter was the hourly fluid removal, which

was changed on 17 (60%) treatments. During 11 (39%) of treatments the blood flow was changed, eight (28%) changed the pre-bloodpump flow, nine (32%) made a change to the ultrafiltrate flowrate and seven (25%) changed the dialysate flowrate.

The median number of changes varied between one and two for each variable. The blood flow rate was changed the most number of times; median 2 (2-6), and the pre-bloodpump flow rate was changed the least number of times; median 1(1-2).

We used linear models to test whether any of the variables (runtime, weight, blood flowrate, pre-bloodpump flowrate, replacement fluid flowrate, dialysate fluid flowrate and fluid removal rate) were significantly related to the effluent rate in the prospective cohort. Starting from the saturated model, we used stepwise backward selection to remove any non-significant variables. The only significant predictor of the effluent rate in the prospective cohort was weight, each one kilogram increase in weight was associated with a decrease in effluent rate of 0.053ml.kg^{-1}.hr^{-1} (p-value 0.04, 95% confidence interval 0.0023 to 0.10). A residual analysis showed that the model appeared to fit the data well, although there is likely to be low-predictive power from it, the adjusted R^2 of the fit being 0.12.

Discussion

The study has proven its primary endpoint. The calculator achieved a median effluent flow rate of 26.8ml.kg^{-1}.hr^{-1} (25.2-29.0ml.kg^{-1}.hr^{-1}). This is an absolute reduction of 14.2ml.kg^{-1}.hr^{-1} from 41.0ml.kg^{-1}.hr^{-1} and the reduction in the variance was highly significant (p<0.0001). This proves that we have achieved our aim to introduce a spreadsheet calculator that is easy to use and successfully recreates flow rates that have been shown to deliver adequate clearance. [5] The reduction in variance of the prescriptions used indicates a more consistent approach to delivering CVVHDF as guided by previous evidence and has proved a valuable educational tool on our critical care. Removing human factors is important as critical care units in the UK are increasingly staffed by junior doctors without a background in intensive care, who rotate frequently.

We attribute the significant increase in the treatment times from 8.5hr to 22.2hr (p=0.0003) to ensuring that the filtration fraction remained below 15%. Limiting fluid replacement according to weight and haematocrit prevents haemoconcentration within the filter and prolongs filter life. Further requirements for clearance are met with dialysate. Longer treatment times are more efficient at delivering CVVHDF as there are fewer periods spent without CVVHDF. The benefit to the patient increases as they receive greater clearance and lose less blood, whilst there is also a reduced cost of filter sets. Reducing the blood flow rate ensured that there were no filters that lasted less than one hour and represents a major improvement in practice. It is noted that the median treatment time is 22.2 hours which is still below the maximum time per filter of 72 hours. However treatments are stopped for other reasons such as being no longer required, or because the patient is transferred off the unit. The total effluent per treatment increased despite the marked reduction in the effluent flow rate. This reflects the increased treatment time and likely reflects an increase in the plasma clearance per 24 hours.

Changes to the CVVHDF prescription occurred despite the use of the calculator. The most commonly changed (60% of treatments) was the hourly fluid removal rate. This was expected as this will change according to clinical need. Changes to the replacement and dialysate rates would change the clearance. The fact that the median effluent rate is 26.8 ml.kg^{-1}.hr^{-1}, not the

intended 25 ml.kg^{-1}.hr^{-1} indicates that these rates were increased, most likely guided by the patient's biochemistry. Thirty-nine percent of the treatments saw an adjustment of the blood flow rate. This is more concerning as it directly effects the filtration fraction. It may explain why changes were made to the pre-bloodpump dilution (28%) that may be required if the blood flow rate has been reduced too much. It is reassuring that whilst the median treatment time increased to 22.2hr the median number of changes for any of the flow rates was two.

Pisitkun [10] initially designed and validated a calculator with the purpose of determining the clearance achieved by renal replacement therapy across a number of modalities. Having been validated, the calculations were then used to test a number of different modalities of RRT including CVVHDF [11]. They used it to assess the adequacy of the clearance and filtration fraction for the flowrates that they had decided to use. They did not start with a desired dose and use it to predict the flow rates necessary to achieve it. Banks (12), described a similar calculator to ours, which he used on his unit. The main difference between our calculator and his was that he kept the dialysate and ultrafiltrate rate the same thereby producing a quadratic equation which gave an effluent flow rate to produce a desired clearance. Blood flow rates were variable and no attention was paid to filtration fraction. We took a different approach based on the audit of our previous practice. We fixed our blood flow rate and filtration fraction so as to determine replacement rates. Haemoconcentration is less likely to occur and so circuit longevity should be increased when the filtration fraction remains below 15%. Dialysate was added to provide a total effluent flow rate of 25ml.kg^{-1}.hr^{-1}.

There are problems with this study. It was not randomised or blinded. The calculator had been introduced into clinical practice and audit had been used to improve its usability. It was seen to bring about improvement and so it would have been unethical to withdraw it from practice in order to randomise. The educational elements were also changing practice. It was not possible to blind practice because of the nature of the intervention. Using historical controls introduces bias and it possible that other improvements in practice occurred during that time. It is also possible that the CVVHDF was optimised in other ways because of the study conditions; line positions could have been optimised, treatments not "electively" stopped and more attention given to anticoagulation.

The study was a pragmatic one and alterations to the prescription were allowed. This requires further study. Improving our understanding of why changes are made will provide users with clearer instructions on how to change the prescription. Future additions to the calculator could include heparin or citrate infusions. If future randomised controlled trials mandate a change in CVVHDF flowrates, then the calculator equations can be changed and the change introduced immediately without further staff training. This is an additional improvement to change management.

We have proven that our calculator significantly reduces variation in prescriptions of CVVHDF and provides an evidence-based dose. It is easy to use and provides personal care for patients whilst optimizing CVVHDF delivery and treatment times.

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Appendix 1.The Calculations

The initial premise is that the filtration fraction (F.F) should be not more than 20% of the circuit plasma flow. For all patients the calculation uses a filtration fraction of 15% of total plasma flow.

Equation 1. Plasma flow (Q.pl) =Total blood flow x (1-Hct).

We deliver CVVHDF using the Prismaflex (Gambro) machine which delivers a filterflux of:

Equation 2. Filterflux =Postfilter fluid replacement (Q.post)+ Fluid removal rate (Q.r)

Pre-filter fluids are pumped into the circuit to prolong filter life, ("pre-dilution"), and this fluid becomes part of the plasma flow.

Equation 3. Total plasma flow = Plasma flow (Q.pl) + Predilution (Q.pre)

Combining these equations:

Equation 4. Filtration fraction= Q.post + (Q.r/Q.pl) +Q.pre

Or, reorganising this:

Equation 5. Qpl = (Q.post +Q.r)/FF – Q.pre

To convert this to the minimum blood flow (BFmin) setting then multiply Q.pl by 1/1-Hct.

Equation 6. BFmin = [(Q.post+Q.r)/FF-Q.pre]x(1/1-Hct)

The second premise in delivering the dose is that the fluid replacement (Qrep), the dialysis fluid flow rate (Qdial) and the removal rate (Qr) should also deliver an adequate dose based on the standard dialysis formula of Kt/Vd = 1.4. If it is assumed that the percentage of patient weight that is body water is 60% then this also equates to a total effluent of $25ml.kg^{-1}.hr^{-1}$ when CVVHDF runs continuously.

Equation 7. K = Qrep + Qdial

Where Qrep = replacement rate and Qdial = dialysate rate.

Equation 8. Kt/Vd = (Qrep + Qdial + Qr) x time / Mass x 0.6 x 1000

Where mass=Kg, 0.6 represents 60% water volume and multiplying by 1000 converts the volume to millilitres. The Prismaflex machine automatically delivers the hourly removal in addition to the replacement fluid. Therefore:

Equation 9. Total effluent (Qrep + Qdial + Qr) = (1.4 x Mass x 0.6 x 1000)/t

The filtration fraction is calculated from the amount of fluid removed from the plasma, in this case Qrep and Qr. The dialysate does not remove a volume of fluid from the plasma, but we assume complete clearance of solutes across the membrane. (This holds true for urea but may

not be true for other toxins or drugs). If the filtration fraction remains constant, the replacement is therefore governed by the blood flow. Rearranging Equation 6:

Equation 10. Qrep = ((((BFmin x (1-Hct)) + Qpre) x 0.15) - Qr

The dialysate makes up the remainder of the total effluent and does not affect the filtration fraction.

Equation 11. Qdial = Total effluent - Qrep - Qrem

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Table 1. Demographic data after introduction of the calculator. Several patients had multiple treatments.

Variable	Post Calculator Group
Records; n	28
Patients; n	15
Age; year*	62.2 ± 13.8
Weight; kg	98.2 ± 38.8
Apache 2†	22.9 ± 5.5
LOS; day‡	5.0 (3.0-20.7)
Outcome Alive; n (%)	11 (73%)
Outcome Death; n (%)	4 (27%)

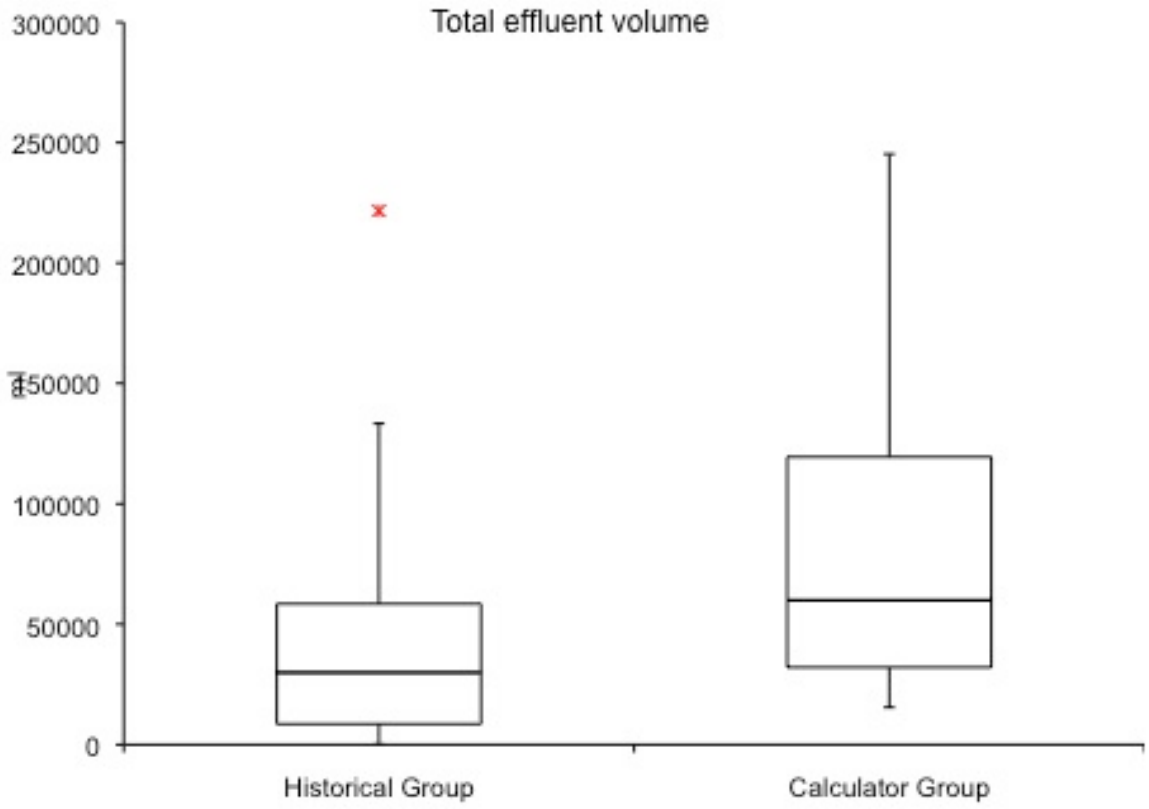
*Mean±SD, †n ± SD, ‡Median (IQR).

Table 2. Flow rate and runtimes collected from the electronic data cards. All data are median (IQR).

Variable	Historical	Post Calculator	P value
Flow rate; $ml.kg^{-1}.hr^{-1}$	41.0 (29.0-89.0)	26.8 (25.2-29.0)	<0.0001
Total effluent; L	29.9 (8.6-111.0)	60.0 (32.1-119.4)	<0.00001
Treatment time; hr	8.5 (2.8-23.0)	22.2 (16.5-44.6)	0.0003

Table 3. The number of treatments in the prospective group in which a treatment was changed after the calculator, and how many changes occurred. Data presented as median (IQR).

Variable	Treatments changed, n (%)	Number of changes per treatment, n
Blood flowrate	11 (39)	2 (2-6)
Pre-Bloodpump flowrate	8 (28)	1 (1-2)
Replacement fluid flowrate	9 (32)	1 (1-3)
Dialysate fluid flowrate	7 (25)	2 (1-3.5)
Fluid removal rate	17 (60)	2 (1-3)


Total effluent volume
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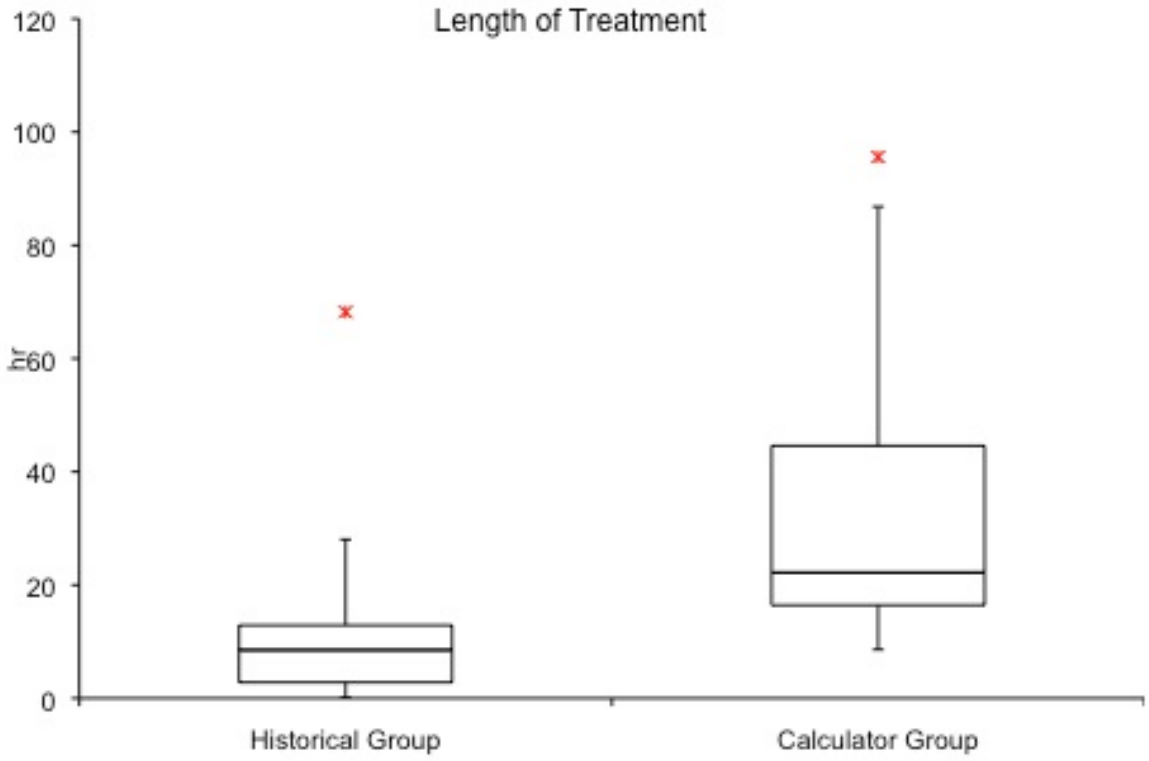
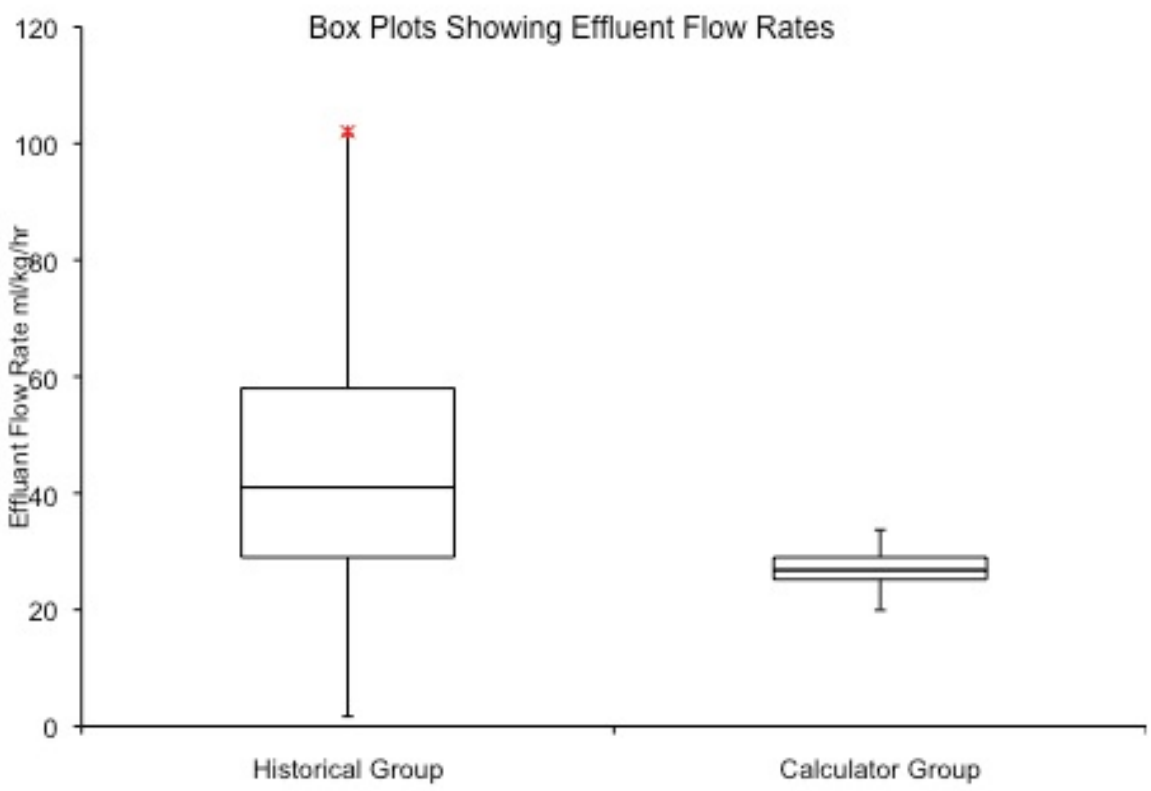
250000
200000
150000
100000
50000
0
Historical Group
Calculator Group


Length of Treatment
120
100
80
60
40
20
0
hr
Historical Group
Calculator Group


Box Plots Showing Effluent Flow Rates
Effluant Flow Rate ml/kg/hr
120
100
80
60
40
20
0
Historical Group
Calculator Group