Could Patient Controlled Thirst-driven Fluid Administration Lead to More Rapid Rehydration Than Clinician-directed Fluid Management? An Early Feasibility Study

Running title: Patient Controlled Fluid Administration

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Abstract

Background: Fluid management is a major factor determining perioperative outcomes, yet in reality fluid administration practice is variable. Thirst however, is a highly sensitive and reliable indicator of fluid deficits. We explored the use of thirst sensation to trigger IV fluid boluses to guide individualised fluid management.

Method: We performed a randomised double crossover trial on 16 healthy male volunteers, of mean age 31.2 years and BMI 24.4kg/m^2. Twice, after administrations of oral Furosemide (40mg) and 12 hours of oral fluid restriction, subjects received a 4-hour IV fluid infusion. In the experimental arm, subjects pressed a trigger to relieve their thirst; administering a 200ml bolus. In the control arm IV fluid was infused following NICE guidelines at 1.25ml/kg/hr with a clinician delivered 500ml IV bolus in response to clinical signs of dehydration. Plasma osmolality and urine specific gravity were measured before and after each infusion.

Results: More fluid was infused in response to thirst than by adherence to NICE guidelines, with a mean difference of 743ml (p=0.0005). Thirst-driven fluid administration was fitted to an exponential function of time, plateauing after a mean half-life of 98.8min. In the experimental arm there was a greater reduction in urine specific gravity and thirst score with mean differences 0.0053g/cm^3 (p=0.002) and 3.3/10 (p=0.003) respectively. Plasma osmolality demonstrated no fluid overload.

Conclusion: A system delivering IV fluid in response to subjective thirst corrects fluid deficits in healthy subjects. A clinical feasibility study will assess the potential use of this system in the perioperative setting.

Dehydration is associated with an increased risk of suffering acute kidney injury,[1] myocardial infarction,[2] venous thromboembolism[3] and delirium.[4] On the other hand, iatrogenic fluid overload is associated with an array of clinical risks including pulmonary and gut wall oedema, intestinal ileus, impaired coagulation, urinary retention and impaired stroke volume.[5] Thus both excessively restrictive and liberal fluid administration may be associated with harm.[6,7] Careful fluid management, which maintains euvolaemia throughout the perioperative period minimises gut injury, facilitating early oral fluid intake, and mobilisation in line with enhanced recovery pathways.[8, 9]

Goal directed fluid therapy, guided by measurements of stroke volume variation, cardiac output, and pulse contour analysis, can reduce both post-operative morbidity and length of stay.[7,10] This intensive monitoring is mostly reserved for the highly-regulated environment of the operating theatre or high-dependency unit, while at other points in the perioperative period, no single gold standard test exists that accurately indicates hydration status.[11] The commonly used clinical features of dehydration represent a poor guide to fluid administration, only appearing when fluid losses exceed 4-5%.[12,13] The diagnosis of dehydration based on clinical signs is therefore unreliable, with very low sensitivity of between 0 and 44%, and poor specificity.[14] Consequently, perioperative fluid management is often highly variable and suboptimal,[15] often delegated to junior staff while physical access to oral fluids is limited.[16] While there is substantial literature regarding perioperative goal directed therapy, the same meticulous investigation has not been applied to broader ward based settings.

Elevated plasma osmolality (pOsm) may represent the best objective index of dehydration in hospitalised patients,[17] with a value >295 mOsm l^{-1} increasingly selected as a defining reference for dehydration.[18] In adults across all ages, and in both sexes, there exists a specific threshold value of pOsm, above which central osmoreceptors linearly increase the sensation of thirst.[19-24] The thirst response is also stimulated by reductions in intravascular volume. The reduced renal artery baroreceptor activity stimulates thirst by increasing serum angiotensin II [25] while reduced atrial and pulmonary arterial baroreceptor activity stimulate thirst either through reductions in tonic atrial natriuretic peptide release [26] or through a shared vagal and glossopharyngeal pathway.[27] This baroreceptor pathway converges with afferents from central osmoreceptors on the hypothalamic thirst centre. Reductions in intravascular volume interact synergistically with increase in pOsm to drive thirst.[28] The stimulation of thirst occurs in response to an integration of physiological parameters and could provide valuable feedback pertaining to a patient's overall fluid balance.

Patient-controlled analgesia (PCA) systems have successfully demonstrated the effectiveness of utilizing subjective discomfort to titrate an intravenous analgesic therapy.[29] Therefore, we hypothesize that the sensation of thirst could similarly be used as a guide to titrate intravenous fluid therapy within strict upper limits. As the first step in testing this hypothesis, we performed a randomised controlled double crossover study on healthy adult volunteers. This lab based early feasibility study serves as a precursor to a clinical feasibility study in perioperative setting.

Methods

The study was completed with local institutional (University College London, UCL) research ethics committee approval (Ref: 9339/001). All subjects provided written, informed consent prior to the study. Inclusion criteria were: males aged 18 – 65 years, American Society of Anaesthesiologists physical status I, body mass between 55 – 100 kg and not on regular medication.

Dehydration Protocol

Subjects avoided strenuous exercise for 48 prior to each trial. Subjects were instructed to take 40mg of the oral loop diuretic, furosemide at 20.00hrs the evening before study, and then to abstain from all fluid, food and caffeine intake until the end of study. Subjects completed this dehydration protocol on two occasions, 7-14 days apart. Subjects were requested to record their pre-diuresis body mass where possible.

Rehydration Protocol

Subjects attended our laboratory at 08.00hrs on the morning after their diuresis and fluid restriction. On arrival, subjects provided an initial urine sample, and their height and weight were documented. Having lain recumbent for 15 minutes, an 18 gauge cannula was placed in a large forearm vein, from which a 5ml blood sample was drawn.[19] A balanced electrolyte solution (4% glucose in 0.18% sodium chloride) was then administered via an Infusomat® Space volumetric pump (B Braun, Melsungen, Germany) over 4-hours. At the start of the infusion, and at 60 minute intervals thereafter, subjects were weighed and asked to mark a 125 millimetre visual analogue subjective thirst scale (ranging from 'not thirsty' to 'extremely thirsty')[19]: dividing the distance marked by 12.5 gave a thirst score out of 10. At the end of the 4-hour trial, a second 5ml blood sample was taken. Subjects voided their bladder 30 minutes before the end of trial and a final urine sample was taken at the end of the trial. Urine samples were immediately analysed for specific gravity with Multistix Reagent Strips (Siemens, Berlin, Germany). Blood samples from the beginning and end of the trial were collected into serum separating tubes and immediately centrifuged; 1.5ml of serum were taken and frozen at -82°C, and later analysed for plasma osmolality by a blinded investigator using freezing point depression (3320 Osmometer: Advanced Instruments, Massachusetts, USA).

In an unblinded, randomised double-crossover design trial, one of two infusion protocols was used at each visit, the order being determined by block randomisation using the R 'blockrand' package.[30]

In the control arm of the trial, according to the National Institute for Health and Clinical Excellence (NICE) guidelines for a patient with an unknown fluid deficit[16], subjects received a continuous infusion of IV fluid at a rate of 1.25ml kg^{-1} hr^{-1}. Subjects were examined for signs of hypovolaemia: prolonged capillary refill time (>2 seconds), reduced skin turgor, systolic blood pressure of <90 mmHg and heart rate of >100 beats per minute. If any of these signs were observed a clinician triggered bolus of 500ml IV fluid would be administered at a rate of 1200ml hr^{-1}.

In the experimental arm of the trial, subjects received thirst-based self-administrated IV fluid boluses. Subjects were instructed to activate a hand-held trigger to relieve their thirst. In response to this trigger, linked to a laptop computer, an auditory alarm sounded and a 200ml fluid bolus was delivered. Data relating to time and volume infused were directly stored in data handling software, R. Cannula patency was maintained by a background infusion rate of 1ml hr^{-1}.

Data handling

Statistical power calculations were estimated with equivalence limits for the difference in volume administered set at 750ml, with a hypothesised standard deviation of 1000ml. To achieve a

5% significance level and 80% power for a two tailed t-test between dependant means, it was calculated that a total sample size of 16 was required.

The primary outcome measure was the difference in the volume of IV fluid administered over the course of each infusion. As secondary outcome measures, differences in urine specific gravity, pOsm and subjective thirst score between the beginning and the end of each infusion were compared between the two arms of the trial for each subject.

The data for volume administered were normally distributed and were thus analysed using a paired t-test. Additionally, the volumes administered over time was logged and fitted to an exponential model in R. Urine specific gravity and pOsm were compared with a paired t-test. Subjective thirst data were not normally distributed and so were compared with a Wilcox signed rank test.

Results

Of 19 subjects who volunteered for our study, two did not meet inclusion criteria, and one subject dropped out due to time constraints. Thus 16 subjects were studied (mean ± SD age 31.2 ± 8.7 years, height 181 ± 6 cm, weight 79.2 ± 11.9 kg, and body mass index 24.4 ± 4.5 kg m^{-2}). The self-reported pre-diuresis body masses of 8 subjects estimate a total body water loss as a result of our dehydration protocol of between 1 – 1.5 litres.

Volume of fluid administered

No subjects required additional fluid administration based on clinical examination. One subject in the experimental arm suffered a brief vasovagal response to cannula placement, which was not treated with fluids and from which they rapidly and spontaneously recovered.

Subjects in the experimental arm who controlled their own administration of IV fluids received 1 138 ± 424 ml. This was significantly greater than the 394 ± 61 ml received in the control arm, with a mean difference of 743 ml (p=0.0005) *[Table 1].*

The mean half-life of the infusions in the experimental arm was 98.8 ± 65.2 minutes *[Figure 1].* In keeping, measurements of the subjects' body mass showed a mean increase in the experimental arm of 1 142g (±440g), with 77.3% (±15.1%) of this increase occurring over the first 120 minutes of the infusion.

Physiological parameters

A larger reduction in urine specific gravity and subjective thirst score was seen over the course of the experimental arm, with mean difference of 0.0053 kg m^{-3} (p=0.002) and 3.3 ± 2.8 (p=0.0034) *[Figure 2]*. Whilst numerically larger reductions in pOsm were associated with the experimental arm, this difference (mean 1.9 mOsm l^{-1}) was not statistically significant.

Discussion

The graph of volume administered against time *[Figure 1]* demonstrates the performance of the experimental arm as compared to the control arm. Clinical signs of dehydration lacked the sensitivity to detect the 1-1.5 litres of fluid loss experienced by the subjects. No additional fluid boluses were administered in the control arm (red), and therefore it appears graphically as a continuous infusion varying only with each subjects' body mass. In the experimental arm (green), subjects quickly self-administered IV fluid over the first 2 hours of the study, largely correcting their fluid deficit. This is reflected by the high proportion (77.3%) of the body mass increase measured, occurring in the first 120 minutes of the study and is consistent with subjects reducing their rate of IV fluid administration as the sensation of thirst subsided in response to rehydration. The volumes administered *V* in the experimental arm were fitted to an exponential function of time *t.*

$$V(t) = \Phi_A - \Phi_B \cdot e^{-\kappa t} \tag{1}$$

Φ_A & Φ_B each approximate to the total volume administered in each subject. This function can be applied to each subject's infusion individually or to the cohort as a whole *[Figure 1b]*. The decay constant κ for each subject corresponds to a mean half-life of 98.8 ± 65.2 minutes. This half-life of thirst driven fluid administration allows for correction of the fluid deficit, after two half-lives. This represents an acceptable timeframe to continue IV fluid therapy following major surgery, especially in those patients with impaired oral intake.

Our subjects reduced their frequency of IV boluses triggering, following infusion of IV fluid and an exponential reduction in subjective thirst scores *[Figure 3]*. The thirst scores (S) in the experimental arm can be fitted to a similar function of time t, as above.

$$S(t) = \Omega_A + \Omega_B \cdot e^{-\lambda t} \tag{2}$$

Ω_A & Ω_B each approximate to the initial thirst intensity prior to rehydration. The similarity of these two functions, which correspond very closely to the raw data, suggests that the sensation of thirst is responsive to rehydration in the time domain; this is essential in avoiding volume overload. There are several potential mechanisms underlying this responsiveness. The reduction in pOsm, towards the threshold of thirst activation, reduces the frequency of osmoreceptor depolarisation.[31] Additionally, the restoration of intravascular volume relieves the additional potentiation of osmoreceptor-stimulated thirst, caused by the convergent baroreceptor pathway.[28] The inhibition of thirst caused by the tonic release of atrial natriuretic peptide, stimulated by normal atrial filling, also contributes to the appropriate subsidence of thirst as intravascular volume is restored.[26] A mean final pOsm of 283.8 mOsm/L following the experimental infusion is consistent with results from previous trials[19-23] which investigated the pOsm threshold for thirst sensitisation. In our study, the lowest final pOsm for any subject was 275 mOsm/L and no subjects had a pOsm outside of the normal reference range. High urine specific gravity is indicative of dehydration, as arginine vasopressin increases the reabsorption of water at the distal convoluted tubule and collecting duct.[32] The reductions in this parameter demonstrate the correction of dehydration.

Values of pOsm were affected by the administration of furosemide, a loop diuretic, which blocks the reabsorption of sodium & potassium in the thick ascending limb of the loop of Henle.[33] The resulting natriuresis led to a lower starting pOsm than would be seen in the pure water loss dehydration more prevalent in the clinical setting, which follows prolonged fasting and use of bowel preparation. Therefore, our study is limited in that the increase in pOsm following diuresis was of a smaller magnitude than would be seen in perioperative dehydration. However, due to the synergistic sensitisation of the osmotic thirst response by the hypovolaemic thirst response, a significant thirst stimulus existed to drive fluid administration. The first clinical feasibility study will assess the thirst response in the context of clinical dehydration. It must be noted that the 4% glucose 0.18% sodium solution used had as osmolality of 282mOsm/L, which is below the threshold for thirst stimulation. If a hypertonic solution, such as 'normal' saline, was used in this

trial there would have been an increase in osmotic thirst throughout the infusion, with a risk of volume overload. Similarly, Ringer's lactate, with a sodium concentration over 4 times higher than the fluid used in this trial would pose a risk of thirst stimulation, as sodium is the primary thirst-stimulating osmolite. The exact bolus volume delivered is likely to affect the performance of this system. Changes in thirst do not occur immediately with rehydration, and therefore larger bolus sizes increase the risk of 'overshooting' the point of zero thirst. Conversely, very small fluid boluses may cause a patient to find the system ineffective, and would require excessively frequent triggering to achieve euvolaemia. In this case a 200 ml bolus, similar to a small glass of water, was chosen as a volume which was likely to be effective. This relatively large bolus size carries a risk of upwardly skewing the volumes in the experimental arm.

Our findings are consistent with previous work on the clinical signs of dehydration, in demonstrating that these signs have low sensitivity for sub-severe degrees of fluid loss.[14] Our study also confirms that thirst is highly sensitive in detecting small variations from euvolaemia. While previous trials focused on purely osmotic stimulation of thirst, with starting osmolalities as high as 310mOsm/L, our study demonstrates the sensitivity of thirst to mild degrees of hypertonicity and mild fluid deficit.[18-22] Most significantly, this trial demonstrates the responsiveness of thirst in the time domain to intravenous rehydration; this is an essential safety aspect of a thirst driven fluid administration system.

There were however several areas of weakness in this trial. Firstly, the study was not blinded. In the absence of a urinary catheter, subjects could not be blinded to the administration of furosemide. Had control arm subjects been given an ineffective thirst trigger in an effort to blind to the experimental arm, its lack of efficacy might have impacted trigger use in the experimental arm. Serial measurements of euvolaemic body mass were not available for each subject, and as such the specific level of fluid deficit in each individual was not known. This is more representative of patients presenting to hospital and accounts for the difference in total volume administered by each subject.

Our findings should be cautiously interpreted across different patient groups. The responsiveness of thirst to changes in fluid balance over short periods of time also varies with age, gender and effects of medications.[20] It has been established that the elderly drink less water in response to a fluid deficit, but owing to the independent thirst inhibiting action of oropharangeal osmoreceptors, it is not yet known if this reduced intake will be seen with intravenous rehydration. This will be a particular focus of further work, in which adjustment of bolus volumes and rates will be investigated as means of compensating for reduced thirst intensity. In pregnancy and in the luteal phase of the menstrual cycle thirst threshold falls.[34] In the clinical setting high doses of morphine appear to stimulate drinking whilst low doses may inhibit the sensation of thirst.[35] Despite the stimulating effect of angiotensin II on thirst activation no changes are seen in thirst rating in response to pain.[36]

In conclusion, our study suggests that thirst is sensitive to mild dehydration and appropriately subsides with intravenous rehydration. The administration of hypotonic intravenous fluid, titrated against the subjective thirst response of a healthy subject, will allow for restoration of approximate euvolaemia, after two half-lives, in an acceptable timeframe of one to six hours. These findings support the study hypothesis that thirst directed patient controlled fluid administration may be feasible as an adjunct to standard therapy. This warrants further investigation in the perioperative setting. We propose a clinical feasibility study of closely supervised patient controlled fluid administration in the postoperative period.

References:

1 Kanagasundaram NS. Pathophysiology of ischaemic acute kidney injury. *Annals of clinical biochemistry* 2015; **52**: 193-205

2 Kloner RA. Natural and unnatural triggers of myocardial infarction. *Progress in cardiovascular diseases* 2006; **48**: 285-300

3 Elias S, Hoffman R, Saharov G, Brenner B, Nadir Y. Dehydration as a Possible Cause of Monthly Variation in the Incidence of Venous Thromboembolism. *Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis* 2016

4 Boettger S, Jenewein J, Breitbart W. Delirium and severe illness: Etiologies, severity of delirium and phenomenological differences. *Palliative & supportive care* 2015; **13**: 1087-92

5 Holte K, Sharrock NE, Kehlet H. Pathophysiology and clinical implications of perioperative fluid excess. *British journal of anaesthesia* 2002; **89**: 622-32

6 Berger Mm Fau - Gradwohl-Matis I, Gradwohl-Matis I Fau - Brunauer A, Brunauer A Fau - Ulmer H, Ulmer H Fau - Dunser MW, Dunser MW. Targets of perioperative fluid therapy and their effects on postoperative outcome: a systematic review and meta-analysis.

7 Voldby AW, Brandstrup B. Fluid therapy in the perioperative setting—a clinical review. *Journal of intensive care* 2016; **4**: 27

8 Lobo DN, Macafee DA, Allison SP. How perioperative fluid balance influences postoperative outcomes. *Best practice & research Clinical anaesthesiology* 2006; **20**: 439-55

9 Zhuang C-L, Ye X-Z, Zhang X-D, Chen B-C, Yu Z. Enhanced Recovery After Surgery Programs Versus Traditional Care for Colorectal Surgery: A Meta-analysis of Randomized Controlled Trials. *Diseases of the Colon & Rectum* 2013; **56**: 667-78

10 Benes J, Giglio M, Brienza N, Michard F. The effects of goal-directed fluid therapy based on dynamic parameters on post-surgical outcome: a meta-analysis of randomized controlled trials. *Critical care* 2014; **18**: 584

11 Armstrong LE. Assessing hydration status: the elusive gold standard. *Journal of the American College of Nutrition* 2007; **26**: 575S-84S

12 Mackenzie A, Barnes G, Shann F. Clinical signs of dehydration in children. *Lancet* 1989; **2**: 605-7

13 Gross CR, Lindquist RD, Woolley AC, Granieri R, Allard K, Webster B. Clinical indicators of dehydration severity in elderly patients. *The Journal of emergency medicine* 1992; **10**: 267-74

14 Fortes MB, Owen JA, Raymond-Barker P, et al. Is this elderly patient dehydrated? Diagnostic accuracy of hydration assessment using physical signs, urine, and saliva markers.

15 Lilot M, Ehrenfeld JM, Lee C, Harrington B, Cannesson M, Rinehart J. Variability in practice and factors predictive of total crystalloid administration during abdominal surgery: retrospective two-centre analysis. *British journal of anaesthesia* 2015; **114**: 767-76

16 Excellence NIfHaC. *Clinical Guidance 174 Intravenous fluid therapy in adults in hospital.* 2013

17 Medicine Io. *Panel on Dietary Reference Intakes for Electrolytes and Water. Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate.*: Washington, D.C. : National Academies Press, 2005

18 Hooper L, Abdelhamid A, Attreed NJ, et al. Clinical symptoms, signs and tests for identification of impending and current water-loss dehydration in older people. *The Cochrane database of systematic reviews* 2015: CD009647

19 Thompson CJ, Bland J, Burd J, Baylis PH. The osmotic thresholds for thirst and vasopressin release are similar in healthy man. *Clin Sci (Lond)* 1986; **71**: 651-6

20 Davies I, O'Neill PA, McLean KA, Catania J, Bennett D. Age-associated alterations in thirst and arginine vasopressin in response to a water or sodium load. *Age Ageing* 1995; **24**: 151-9

21 Pross N, Demazières A, Girard N, et al. Influence of progressive fluid restriction on mood and physiological markers of dehydration in women. *The British journal of nutrition* 2013; **109**: 313-21

22 McKenna K, Morris AD, Azam H, Newton RW, Baylis PH, Thompson CJ. Exaggerated vasopressin secretion and attenuated osmoregulated thirst in human survivors of hyperosmolar coma. *Diabetologia* 1999; **42**: 534-8

23 Stachenfeld NS, Silva C, Keefe DL, Kokoszka CA, Nadel ER. Effects of oral contraceptives on body fluid regulation. *Journal of applied physiology (Bethesda, Md : 1985)* 1999; **87**: 1016-25

24 Baylis PH, Thompson CJ. Osmoregulation of vasopressin secretion and thirst in health and disease. *Clinical endocrinology* 1988; **29**: 549-76

25 Fitzsimons JT. Angiotensin, thirst, and sodium appetite. *Physiol Rev* 1998; **78**: 583-686

26 Burrell LM, Palmer JM, Baylis PH. Atrial natriuretic peptide inhibits fluid intake in hyperosmolar subjects. *Clin Sci (Lond)* 1992; **83**: 35-9

27 Johnson AK. The sensory psychobiology of thirst and salt appetite. *Medicine and science in sports and exercise* 2007; **39**: 1388-400

28 Verbalis JG. How does the brain sense osmolality? *Journal of the American Society of Nephrology : JASN* 2007; **18**: 3056-9

29 Hudcova J, McNicol ED, Quah CS, Lau J, Carr DB. Patient controlled opioid analgesia versus conventional opioid analgesia for postoperative pain. *Cochrane Database of Systematic Reviews* 2006

30 (CRAN) TCRAN. Randomization for block random clinical trials 'blockrand'. 2010

31 Bourque CW, Voisin DL, Chakfe Y. Stretch-inactivated cation channels: cellular targets for modulation of osmosensitivity in supraoptic neurons. *Progress in brain research* 2002; **139**: 85-94

32 Nielsen S, Chou Cl Fau - Marples D, Marples D Fau - Christensen EI, Christensen Ei Fau - Kishore BK, Kishore Bk Fau - Knepper MA, Knepper MA. Vasopressin increases water permeability of kidney collecting duct by inducing translocation of aquaporin-CD water channels to plasma membrane.

33 Paul S. Balancing Diuretic Therapy in Heart Failure: Loop Diuretics, Thiazides, and Aldosterone Antagonists. *Congestive Heart Failure* 2002; **8**: 307-12

34 Spruce BA, Baylis PH, Burd J, Watson MJ. Variation in osmoregulation of arginine vasopressin during the human menstrual cycle. *Clinical endocrinology* 1985; **22**: 37-42

35 Vokes T. Water Homeostasis. *Annual review of nutrition* 1987; **7**: 383-406

36 Farrell MJ, Egan GF, Zamarripa F, et al. Unique, common, and interacting cortical correlates of thirst and pain. *Proceedings of the National Academy of Sciences of the United States of America* 2006; **103**: 2416-21

	Trial Arm		Mean Diff (±SD)	p Value
	Control	Experimental		
Volume (ml)	394	1 138	743 (± 455)	< 0.001
Δ Body Mass	340	1 143	802 (± 517)	< 0.001
Δ Urine SG (kg m^{-3})	0.009	0.014	0.005 (± 0.005)	< 0.01
Δ Thirst	4.5	7.79	3.3 (± 2.8)	< 0.01
Δ pOsm (mOsm L^{-1})	*1.9*	*3.8*	*1.9 (± 2.6)*	*0.14*

Table 1 Comparisons between the effects of the two methods of fluid administration

a
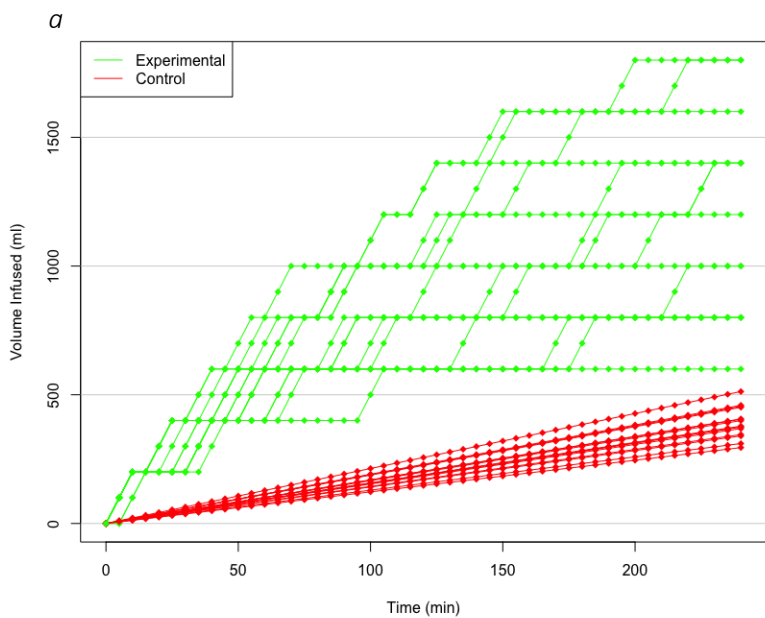
Figure 1 Comparison of fluid administration over the 4 hour infusion between the experimental arm (green) and control arm (red). a) Raw data points for each subject.

b
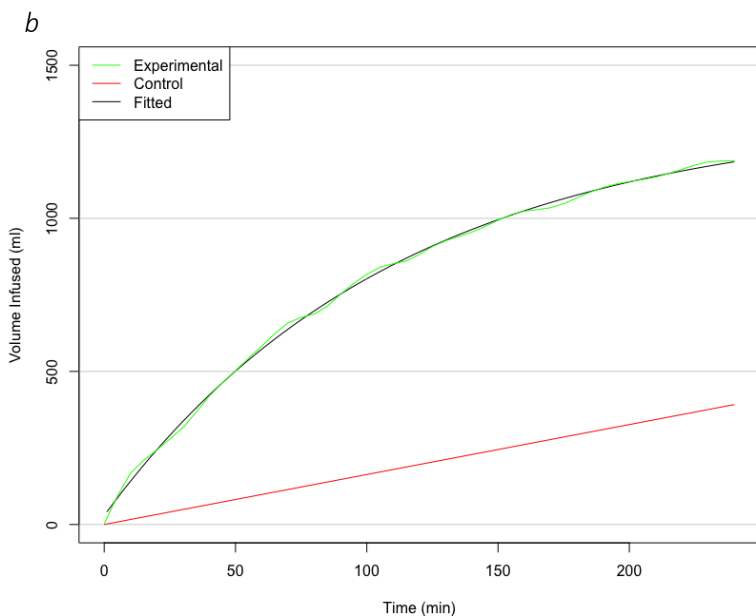
b) Aggregated plots of the data for all subjects. Additionally, the exponential function to which the experimental infusions are fitted is plotted in black.
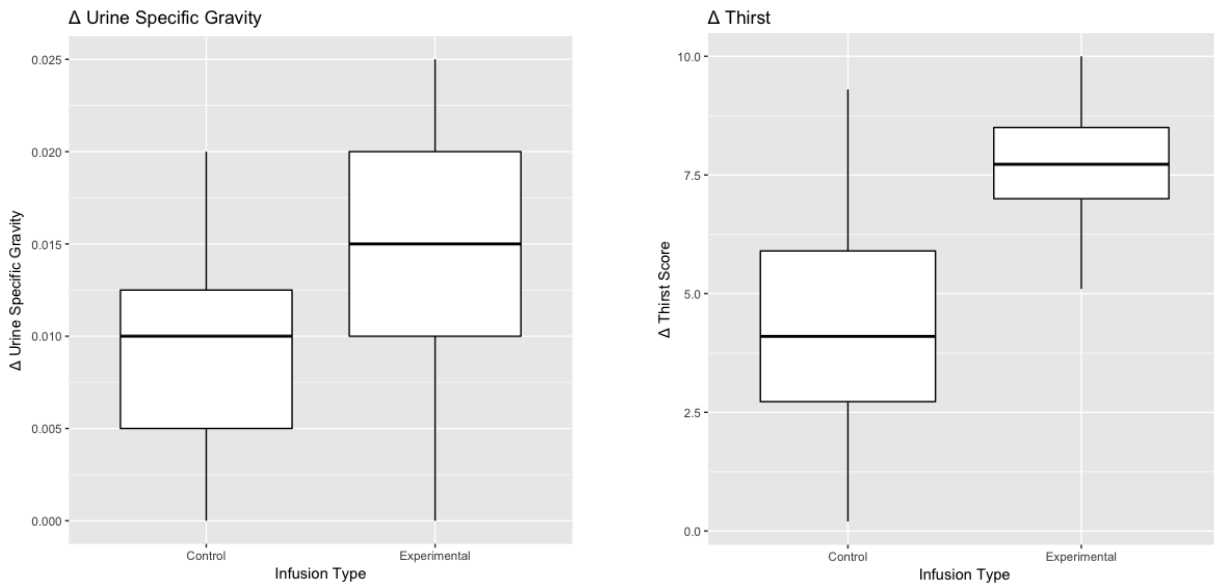
Figure 2 Changes in urine specific gravity (left) and thirst score (right) over the course of each infusion
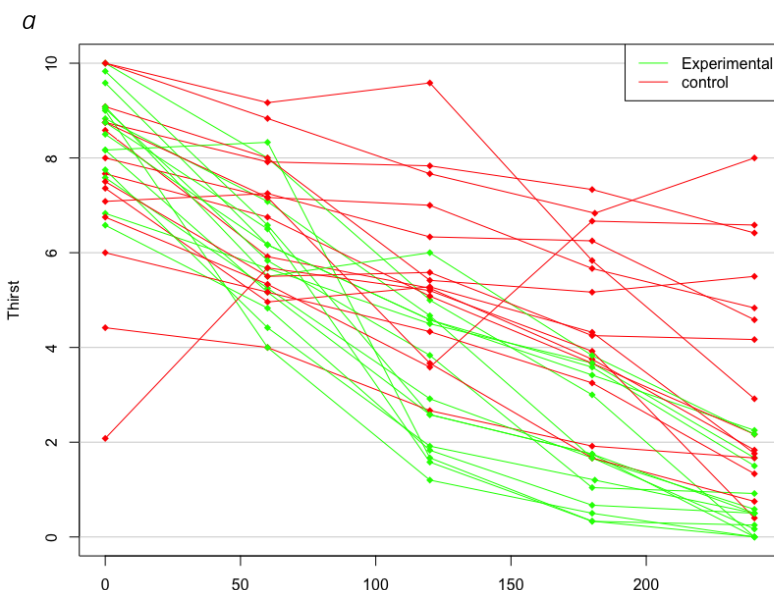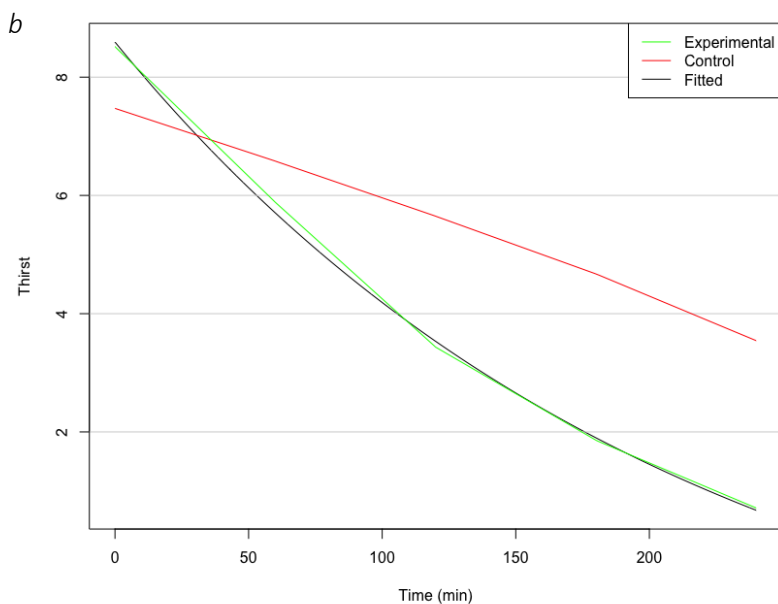

Figure 3 Comparison of subjective thirst scores over the 4 hour infusion between the experimental arm (green) and control arm (red). a) Raw data points for each subject.

b) Aggregated plots of the thirst data for all subjects. Additionally, the exponential function to which the experimental infusions are fitted is plotted in black. The exponential decrease in thirst in the experimental arm corresponds to the exponential decrease in infusion rate seen in Figure 1
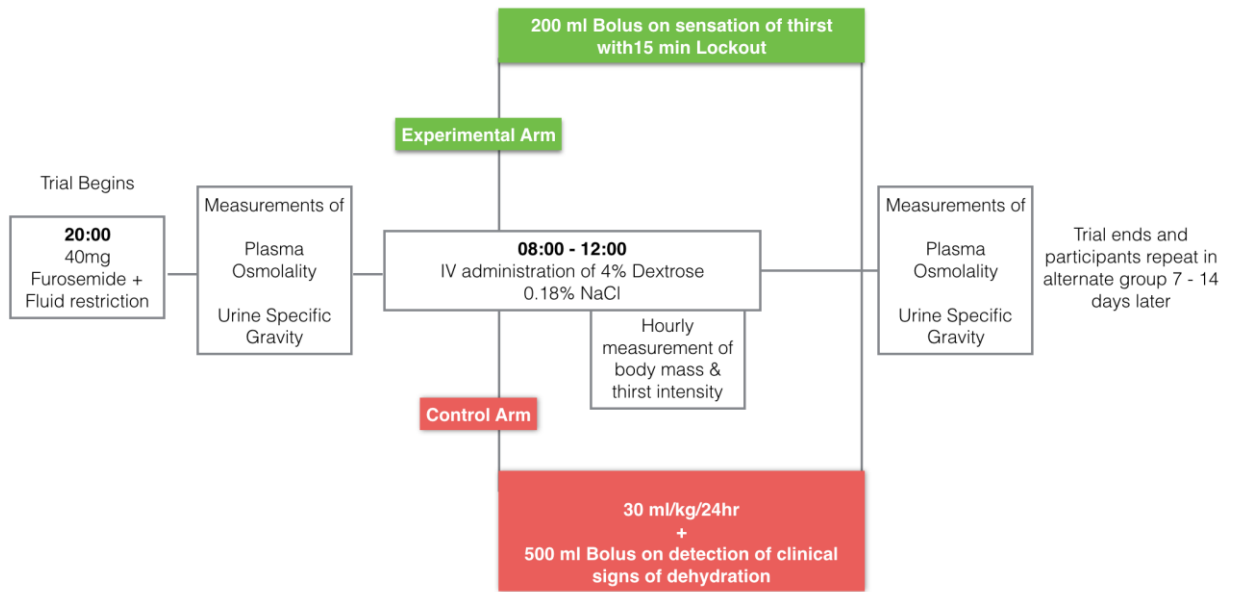
Figure 1** A diagram of the movement of subjects through our experiment. Subjects moved from left to right, passing into either the experimental or control arm, before repeating the protocol in the opposite arm of the trial between 7-14 days later.