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Title: Iatrogenic hypoglycaemia following glucose-insulin infusions for the treatment of hyperkalaemia

Short Title:*Gwl Hypo Evaluation*

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Abstract

Objectives: To study the incidence of, and risk factors for, iatrogenic hypoglycaemia following GwI infusion in our institution.

Context: Hyperkalaemia is a life-threatening biochemical abnormality. Glucose-with-insulin (GwI) infusions form standard management, but risk iatrogenic hypoglycaemia (glucose ≤ 3.9mmol/L). Recently updated UK guidelines include an additional glucose infusion in patients with pre-treatment capillary blood glucose (CBG) <7.0 mmol/L.

Design: Retrospective analysis of outcomes for GwI infusions prescribed for hyperkalaemia from 1st January-28th February 2019, extracted from the Newcastle-upon-Tyne Hospitals NHS Foundation Trust electronic platform (eRecord).

Participants: 132 patients received 228 GwI infusions for hyperkalaemia.

Main outcome measures: Incidence, severity and time-to-onset of hypoglycaemia.

Results: Hypoglycaemia incidence was 11.8**%**. At least 1 hypoglycaemic episode occurred in 18.2% of patients with 6.8% having at least 1 episode of severe hypoglycaemia (<3.0 mmol/L). Most episodes (77.8%) occurred within 3 hours of treatment.
Lower pre-treatment CBG(5.9 mmol/L [4.1 mmol/L - 11.2 mmol/L],; versus 7.6 mmol/L [3.7 mmol/L - 31.3 mmol/L], p = 0.000) was associated with hypoglycaemia risk. A diagnosis of type 2 diabetes and treatment for hyperkalaemia within the previous 24 hours were negatively associated.

Conclusions: Within our inpatient population, around 1 in 8 GwI infusions delivered as treatment for hyperkalaemia resulted in iatrogenic hypoglycaemia. Higher pre-treatment CBG and a diagnosis of type 2 diabetes were protective, irrespective of renal function. Our findings support the immediate change to current management, either with additional glucose infusions, or by using glucose-only infusions in patients without diabetes. These approaches should be compared via a prospective randomised study.

Keywords: Hypoglycaemia, hyperkalaemia, dextrose, glucose-with-insulin

Introduction

Hyperkalaemia is a commonly encountered but potentially life-threatening biochemical abnormality, with a reported incidence of between 1-10% in hospital inpatients, particularly among those with renal impairment [1,2]. Due to the effects of potassium on cardiac myocyte resting membrane potential, hyperkalaemia is associated with a significant risk of developing arrhythmias and cardiac arrest, and potassium (K^+) levels ≥ 6.5 mmol/L (normal range 3.5-5.3 mmol/L) warrant urgent treatment [3]. There is surprisingly limited evidence behind the current guidelines for treating hyperkalaemia in hospital inpatients, and there is wide variation in clinical practice both within and between individual centres.

Glucose-with-insulin (GwI) infusions form part of the current UK national guidelines from the Renal Association for treatment of hyperkalaemia[4], based on the physiological observation that insulin stimulates the activity of the Na^+-K^+ ATP pump, which leads to an influx of potassium into cells and a corresponding reduction in extracellular fluid potassium.

Previous publications have highlighted the risk of iatrogenic hypoglycaemia (capillary blood glucose ≤ 3.9mmol/L) following hyperkalaemia treatment with GwI infusions; the reported incidence ranging from 6% to 75%[5-9]. Patients with hyperkalaemia may have additional risk factors for hypoglycaemia, such as end-stage renal disease, or diabetes treated with insulin or insulin secretagogue therapy. Hypoglycaemia has potentially life-threatening consequences, including precipitation of acute cardiovascular events and cardiac arrhythmia, and may cause life-changing generalised brain injury in the long term. Hypoglycaemia among hospitalised inpatients has also been linked to increased morbidity, mortality and length-of-stay [10].

Consideration of the above evidence has led to some changes in the updated UK Renal Association (UKRA) guidelines (July 2020[11]), which now recommend:

1. Treat all patients requiring GwIwith 10 units of soluble insulin and 25g dextrose
2. In addition, give 10% dextrose at a rate of 50ml/hr for 5 hrs in patients with pre treatment glucose < 7 mmol/L
3. Monitor blood glucose for 12 hrs after GwI treatment

Our aim was to determine the incidence of iatrogenic hypoglycaemia following GwI infusions in our inpatient population, as well as to determine any predictive factors for development of hypoglycaemia.

Methods

We performed a retrospective audit within the Newcastle-upon-Tyne Hospitals NHS Foundation Trust to determine the incidence of iatrogenic hypoglycaemia in adult patients receiving GwI infusions for the treatment of hyperkalaemia. Caldicott approval was granted for data access and the project was registered with the trust Audit registry (Clinical Governance & Audit Registration N$^{o.}$9889). Data on all patients prescribedGwI infusions as treatment for hyperkalaemia from 1stJanuary to 28thFebruary 2019 was extracted from the trust electronic prescribing system "eRecord".

Our trust guidelines recommend treatment with GwI infusion for all patients with potassium level ≥ 6.5 mmol/L, or potassium 6-6.4 mmol/L with ECG changes, or where there are other reasons for concern. GwI as per trust protocol contains 10 units of Actrapid ® (short acting human insulin), infused over 15 minutes, in either 50 ml of 50% dextrose (*i.e.* 25g glucose), or 100ml of 20% dextrose (20g glucose) in patients where there are concerns about the reliability of IV access. Capillary blood glucose (CBG) is recorded at baseline, and at 15 minutes, 30minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours and 6 hours from the onset of the infusion. All patients who developed hypoglycaemia (defined as CBG ≤ 3.9mmol/L) up to six hours following GwI infusions were included in the "hypoglycaemia" cohort, and werecompared against those who did not develop hypoglycaemia.

The following data were extracted from eRecord: age and sex of patient, date and time of infusion, baseline capillary glucose, pre- and post-treatment potassium level and renal function at the time of treatment. Body mass index (BMI) was not available for the majority of patients, as patient weight and height is not reliably recorded during acute admissions within our trust.Previous diagnoses of diabetes (including treatment modality), chronic kidney disease (CKD; defined as a persistent estimated glomerular filtration rate – eGFR of <60ml/min/1.73m^2 in the 3 to 6 months preceding admission) and chronic liver disease were also recorded.The reduction in potassium after treatment was determined from the nadir potassium level within six hours of infusion. Hypoglycaemia was defined as capillary blood glucose <4.0mmol/L, and severe hypoglycaemia as capillary blood glucose of <3.0 mmol/L, based on the National Diabetes

Inpatient Audit definitions[12]. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results were analysed using IBM® SPSS Statistics® (Version 26, Chicago, IL). In univariate analysis for the key outcome of development of hypoglycaemia, continuous variables of interest were compared with independent-samples t-test or Mann-Whitney *U* test depending on their distribution. The categorical variables were analysed with Chi-Square statistic or Fisher's exact test. Analysis of time to hypoglycaemia against renal function was by Kruskal-Wallis test for categorical data (existing CKD diagnosis) or by Pearson correlationfor continuous data (serum creatinine).Results are presented using median and range for continuous variables unless stated otherwise, and with odds ratios with 95% confidence intervals (CI) for categorical variables.

Results

Baseline Demographics

Data was extracted for 132 patients (86 males and 46 females). The median age of participants was 67 years (range: 19-95 years). There was no significant difference in age between males (median: 66 years [range: 23-95 years]) and females (median: 72 years [range: 19-95 years], (Mann-Whitney *U, p* = 0.481). A total of 261 GwI infusions were prescribed for these patients between 01/01/2019 and 28/02/2019for treatment of hyperkalaemia. Thirty threeepisodes of GwI infusions were excluded from analysis due to lack of recorded baseline blood glucose, post-treatment potassium or non-standard time points, leaving 228 infusions (prescribed to 132 patients).

A prior diagnosis of diabetes mellitus was recorded in 37.9% (95% CI: 30.1-46.4%; *n* = 50/132). As expected from a cohort experiencing hyperkalaemia, 54.6% (95% CI: 46.1-62.8%; *n*= 72/132) had an established diagnosis of CKD G3 or above (on basis of prior eGFR).

Incidence and severity of hypoglycaemia

At least one episode of hypoglycaemia occurred in 18.2% of patients (95% CI: 12.5%-25.6%; *n* = 24/132) with 6.82% (95% CI:3.63%-12.45%; *n* = 9/132) having at least one episode of severe hypoglycaemia (<3.0mmol/L).There were 27(11.8%, 95% CI: 8.3-16.7%) episodesof hypoglycaemia within the six hours after treatment recorded among 228 infusions prescribed.

Factors influencing the risk of developing hypoglycaemia

PatientFactors

In univariate analysis, the age (*OR* 0.987/year, 95% CI: 0.960-1.014, *p* = 0.345) and sex (*OR* 2.325, males versus females; 95% CI: 0.806-6.705, *p* = 0.118) of the patient were not significant predictors of having at least one episode of hypoglycaemia following GwItreatment.

In wider univariate analysis of patient-level factors,a prior diagnosis of type 2 diabetes mellitus appeared to be protective against hypoglycaemia (OR 0.079, 95% CI: 0.010-0.616, p = 0.015). A diagnosis of type 1 diabetes, treatment with insulin or a sulfonylurea and degree of chronic kidney disease were not significantly associated with hypoglycaemia(*Table 1*).No patients (0/19) in the hypoglycaemia group had a recorded diagnosis of chronic liver disease, therefore we did not pursue further analysis.

Episode-Level Factors

With the data available, we expressed the following epidemiological data by discrete hyperkalaemia episode, rather than per patient(*Table 2*).

The median pre-treatment glucose was significantly lower in those that developed iatrogenic hypoglycaemia (5.9 mmol/L [range: 4.1 mmol/L - 11.2 mmol/L], *n* = 27; versus 7.6 mmol/L [range: 3.7 mmol/L - 31.3 mmol/L], n = 201; Mann-Whitney *U*, *p* = 0.000). There was a strong association between higher pre-treatment glucose levels and reduction in hypoglycaemia events (*OR* 0.669/mmol, 95% CI: 0.520-0.860, *p* = 0.002). Indeed, the 2020 UKRA guidelines recommend the use of a <7 mmol/L threshold for pre-infusion glucose as being at increased risk of hypoglycaemia[11]. We support the use of this threshold, identifying a strong relationship (*OR* 4.146; 95% CI: 1.676-10.255, *p* = 0.002) between hypoglycaemia and pre-infusion glucose <7 mmol/L(*Figure 2*).

The median number of treatments per patient was 1 (range 1-12),but 34.1% (*n* = 45/132) of patients had more than one treatment episode.The number of treatments across the patient's admission was inversely associated with episodes of hypoglycaemia (*OR* 0.347, 95% CI: 0.123-0.975, *p* = 0.045) following GwI infusion. This may be a marker of insulin resistance in this group.

Whilst there was a slight statistically significant difference between the median pre-treatment potassium it was not a significant predictor in univariate odds analysis of hypoglycaemia (OR 0.402, 95% CI: 0.138 – 1.175, p = 0.096).

Of the infusions prescribed, only 4.4% (95% CI: 2.4%-7.9%; n = 10/228) utilised 20% dextrose, whilst the majority (95.6%) used 50% dextrose. Due to the small number in the first group, and indeed the small difference in administered glucose (20g versus 25g), we have not compared these variables separately.

There were no significant differences foundin age, current renal function, or previous diagnosis of CKD between those developing hypoglycaemia and those who did not. Similarly, there was no difference in potassium response to treatment (*Table 2*).

Time to developing hypoglycaemia

Figure 1demonstratesthat most episodes of hypoglycaemia occurred within the first 3 hours of receiving GwI infusions, with 51.9% of hypoglycaemia episodes occurring within 2 hours, and 77.8% within 3hours of the infusion. The median time to development of hypoglycaemia was 110 minutes (range 35-221 minutes). There were no episodes of hypoglycaemia recorded between 4 and 6 hours after infusion.There was no effect on time to hypoglycaemia demonstrated in patients with existing CKD ($H(3) = 0.669$; $p = 0.880$), or depending on serum creatinine at the time of treatment ($r = -0.09$; $R^2 = 0.008$; $p = 0.677$).

Discussion

The incidence of iatrogenic hypoglycaemia following GwI infusions for hyperkalaemia within our study population was 11.8%, which is similar to the rates (6.1% to 17.5%) reported in other studies (*Table 3*)[6-8,13-16]. The rate of hypoglycaemia we observed was slightly lower than in another recent UK studyby Boughton et al[13]; however, this is most probably because their protocol involved administering 10 units of insulin in a lower (20g) glucose load, whereas 95.6% of the infusions in our cohort contained a 25g total glucose load (as recommended inthe 2014 Renal Association guidelines). Taking into account the number of patients having recurrent infusions, 18.2% of patients (95% CI: 12.5%-25.6%; *n* = 24/132) developed hypoglycaemia after receiving GwI infusions for the treatment of hyperkalaemia which, in our view, represents an unacceptable level of riskto patients.

Lower pre-treatment capillary blood glucose was identified as the main risk factor for development of hypoglycaemia in ouranalysis. A prior recorded diagnosis of type 2 diabetes appeared protective, reflecting insulin resistance in this group.Only one previous study[6] has mentioned this as a potential risk factor, but the study involved patients exclusively with end-

stage renal disease, and therefore generalisability is limited. Our findings show importantly and uniquely, that a diagnosis of type 2 diabetes appears protective regardless of pre-existing renal function.

Several suggestions have been made to reduce risk of hypoglycaemia from GwI infusions[9,17], including administering a lower dose of insulin, pre-loading with additional glucose or administering a higher overall glucose load.

It is evident that graded release of endogenous insulin occurs as part of the normal physiological response to a glucose load[18]. Hence for hyperkalaemic patients without a diagnosis of diabetes or other disorders of insulin regulation, administering intravenous glucose alone is potentially an effective treatment, and eliminates the risk of iatrogenic hypoglycaemia.

A small crossover study by Chothia*et al.* in non-diabetic patients with hyperkalaemia examined this principle. After infusion of 50g dextrose, with- or without- 10 units of insulin, they did find a mean K^+ drop of 0.5 (+/- 0.31) mmol/L with dextrose alone, however this was slightly less than the 0.83 (+/- 0.53) mmol/L reduction in the group treated with conventional GwI (p=0.01)[17]. Although this approach is currently not recommended in the latest UKRA guideline iteration, we would strongly support further investigation of this approach, with a view to future guidelines being multidisciplinary, rather than monospecialty-derived.

We believe there needs to be an immediate change to practice in order to reducethe present unacceptable risk of developing hypoglycaemia with GwI infusions for hyperkalaemia, particularly in patients with a lower pre-treatment glucose level and without type 2 diabetes. However, the question is whether to adopt the proposal in recently updatedUKRA guidelines to administer an additional glucose load of 25g, or more simply, to administer glucose-only infusions for this patient group. We propose that the safety and efficacy of these two approaches be subject to prospective study.In the interim, we propose the following changes (Figure 3) to the hyperkalaemia management protocol within our trust and suggest that this can be adopted by other institutions, due to concerns regarding patient safety with existing protocols as highlighted by our audit.

There were limitations to our analysis. Due to insufficient data, we were unable to perform rigorous within-person risk factor analysis for those who underwent multiple GwI treatments. We did however distinguish factors on aper-patient (e.g. sex) versus per-episode (e.g. pre-treatment

glucose) basis. Examination of whether repeated GwI infusions increased hypoglycaemia risk over a 24-hour time period in fact found the opposite association. This may be another marker of insulin resistance in such patients. Similarly, for patients with diabetes, medication,including insulin injections, given on the same day could theoretically have contributed to greater risk of hypoglycaemia, but we found these patients to have a lower incidence of hypoglycaemia. We did not have sufficient data available to assess whether body mass index affected risk of hypoglycaemia, as patient weight and height are currently not systematically or reliably recorded as part of acute inpatient admissions to our trust.We also did not look at the effect of potential concurrent medication (other than insulin or oral hypoglycaemic medication) with hypoglycaemia listed as a possible side-effect; however there are likely only small numbers of patients on such medication.

The July 2020UKRA guidelines recommend actively monitoring for hypoglycaemia for twelve hours post infusion, which is not our current trust policy. We did not attempt to collect data beyond six hours due to potential for introducing bias (e.g. those with a diagnosis of diabetes would have had additional blood glucose monitoring). Reassuringly, we did not identify any episodes of hypoglycaemia occurring between four and six hours after treatment.

Conclusions

Consistent with previous publications, we determined that around 1 in 8GwI infusions (11.8%) delivered as treatment for hyperkalaemia resulted in iatrogenic hypoglycaemia within our inpatient population, with 18.2% patients (almost 1 in 5) experiencing this complication.

Having a lower pre-treatment capillary blood glucose level was the main factor associated with hypoglycaemia risk, and a prior diagnosis of type 2diabetes may be protective. Our findings support UKRA recommendations for giving additional glucose loading for patients with low pre-treatment glucose level (<7.0mmol/L), but would equally support a robust exploration of using glucose-only infusions. These two approaches should ideally be compared via a prospective randomised study, but for the interim, we recommend the immediate revision of current approaches to hyperkalaemia treatment for overwhelming reasons of patient safety.

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Tables and Figures

Factor	Hypoglycaemia group (n=24)	No hypoglycaemia group (n=108)	Univariate OR	95% CI	*p-value*
Age in years [median (range)][a]	63.0 (19-95)	67.5 (19-95)	0.987/year	0.960-1.014	0.345
Sex (M versus F)[b]	79.2% male (n = 19/24)	62.0% male (n = 67/108)	2.325	0.806-6.705	0.118
Recorded diagnosis of diabetes[b]	20.8% (n=4/24)	42.6% (n=46/108)	0.355	0.123-1.020	0.054
Prescribed diabetes treatment[b]	16.7% (n=4/24)	35.2% (n=38/108)	0.368	0.117-1.156	0.087
Prescribed insulin for diabetes[b]	16.7 % (n=4/24)	25.0% (n=27/108)	0.600	0.188-1.911	0.387
Prescribed sulphonylurea for diabetes[NB]	0 % (n=0/24)	10.2 % (n=11/108)	-	-	-
CKD Diagnosis (Compared with CKD Stages 1 and 2)[b]					
Stage 3	29.2% (n = 7/24)	30.6% (n = 33/108)	1.594	0.572-4.438	0.372
Stage 4	12.5% (n = 3/27)	15.7% (n = 17/108)	1.511	0.407-5.606	0.537
Stage 5	12.5% (n = 3/27)	8.3% (n = 9/108)	1.133	0.212-6.053	0.884

Table 1. Predictors of post-treatment hypoglycaemia – Patient Factors

OR -odds ratio; CI – confidence interval; CKD- chronic kidney disease

Statistical test applied: [a] Mann Whitney U Test, [b]Chi-Square test

[NB] – Chi Square test could not be applied to this variable due to no responses in one group

	Hypoglycaemia (n=27)	**No hypoglycaemia** (n=201)	***p-value***
Median pre-treatment K^+ level *mmol/L*[a](Range)	6.1 (5.2-8)	6.3 (5.4-8.2)	**0.024**
Median pre-treatment CBG level *mmol/L*[a](Range)	5.9 (4.1-11.2)	7.6 (3.7-31.3)	**0.000**
Median creatinine *mmol/L*[a](Range)	246 (53-684)	170 (50-2114)	0.669
Mean maximal reduction in K+ *mmol/L*[b](+/- SEM)	0.77 +/- 0.09	0.74 +/- 0.05	p = 0.779

Table 2. Predictors of post-treatment hypoglycaemia – Episode-level Factors

CBG – capillary blood glucose; SEM – standard error of the mean

Statistical test applied: [a] Mann Whitney U Test, [b] independent samples t-test

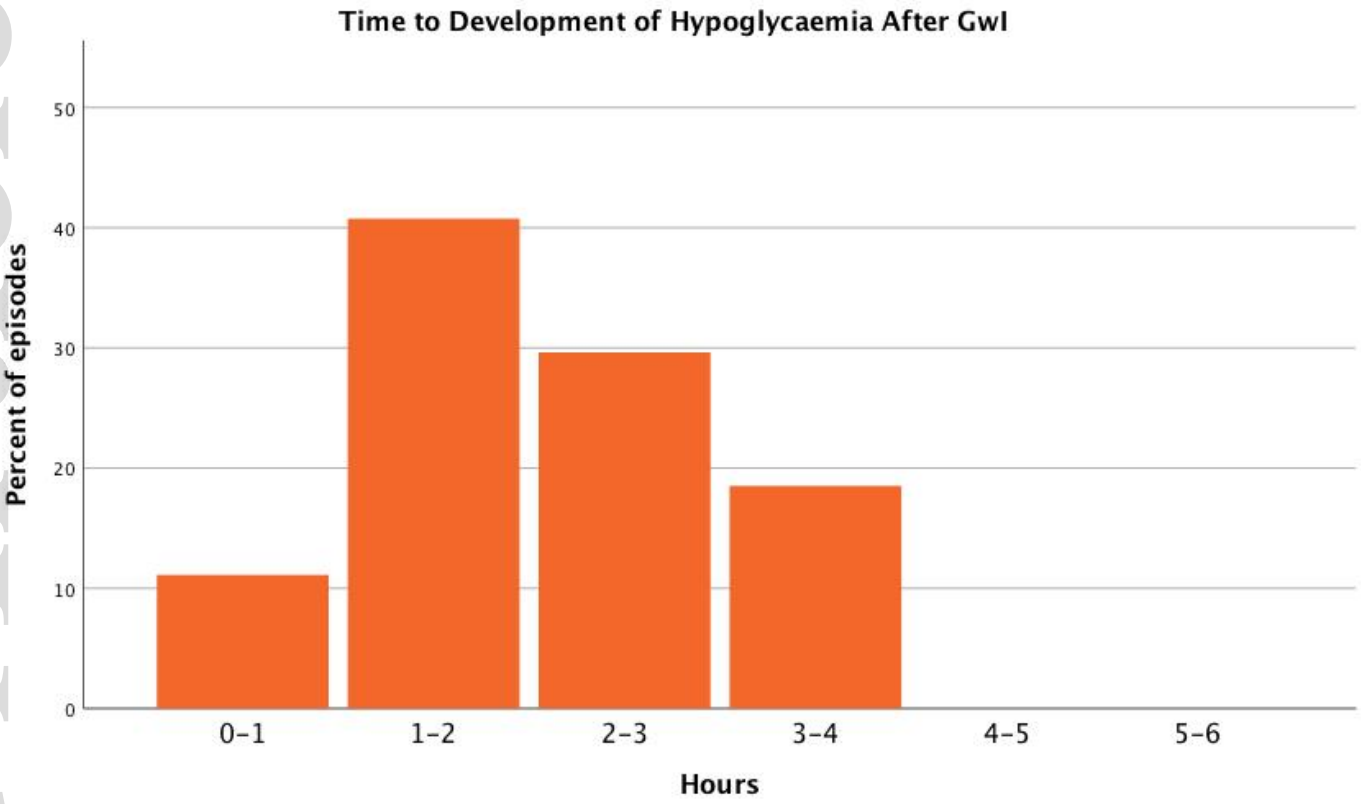


Figure 1. Time to development of hypoglycaemia following GwI infusion

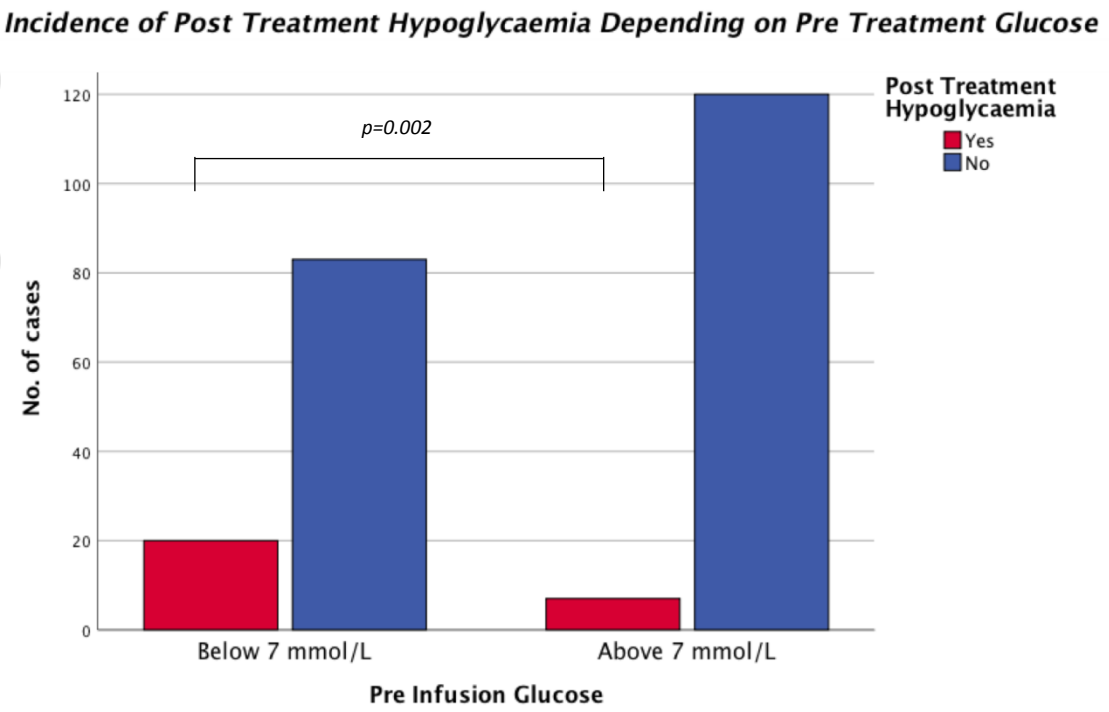
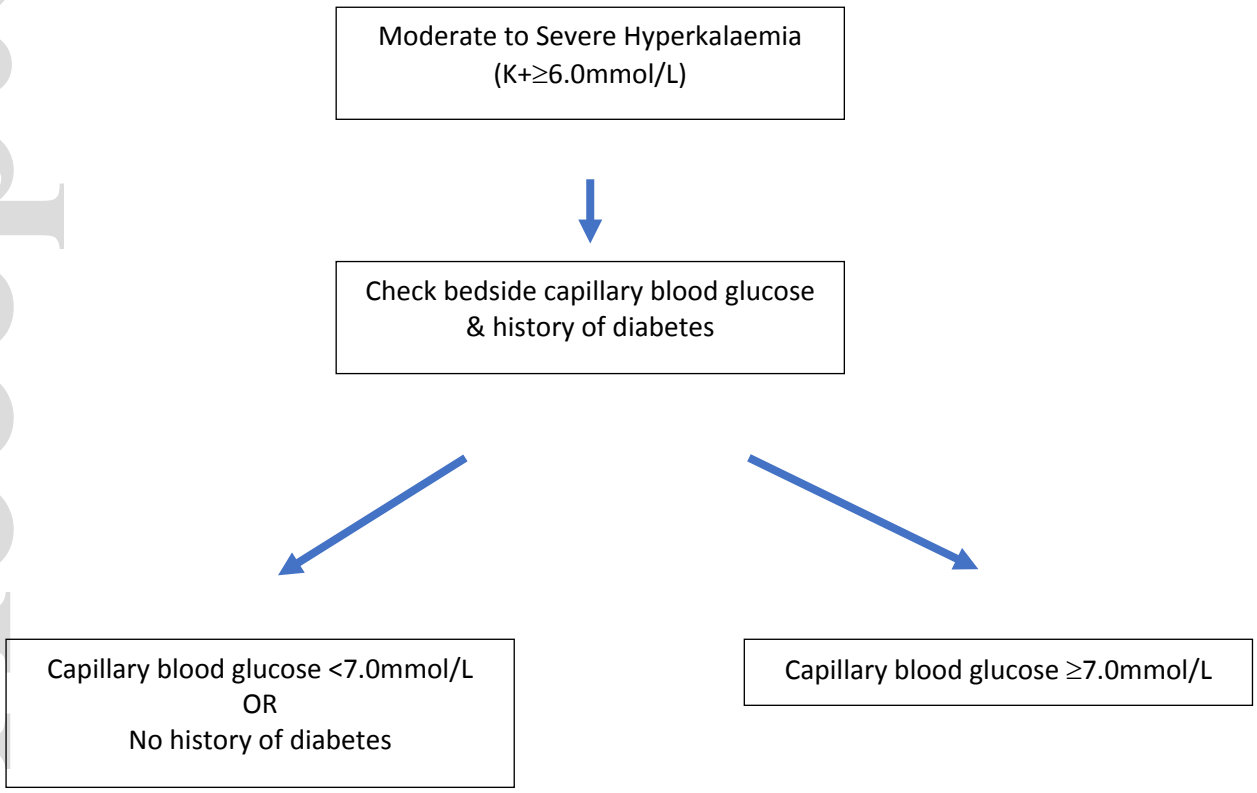


Figure 2. Incidence of Post Treatment Hypoglycaemia with Glucose Above and Below 7 mmol/l

Authors	Publication date	Population	Treatment protocol	% developing hypoglycaemia	Identified Risk Factors	Limitations
Apel et al[6]	2014	Inpatients on haemodialysis (USA) (n = 221 episodes)	10 units insulin + 25g dextrose (94%)	13.1% (29/221 episodes)	Absence of DM Not taking medication for DM Lower pre-treatment glucose	Hypoglycaemia defined as CBG <3.3 mmol/L Did not distinguish type of DM Haemodialysis patients only Analysed "per episode", not "per patient"
Boughton et al[13]	2019	Adult (non critical care) inpatients (UK) (n = 662 episodes)	10 units insulin + 20g dextrose	17.5% (116/662 episodes)	Older age Low body weight Lower pre-treatment glucose	Did not distinguish type of DM Analysed "per episode", not "per patient"
Coca et al[7]	2017	Adult (non haemodialysis) inpatients (Spain) (n = 164 episodes)	10 units insulin + 50g dextrose + 40mg furosemide	6.7% (11/164 episodes)	Lower pre-treatment glucose	No factors reached significance Did not distinguish type of DM Analysed "per episode", not "per patient"
Estep et al[14]	2015	All adult inpatients (USA) (n= 86)	Variable dose of both insulin and dextrose	17.4% (15/86 patients)	Lower pre-treatment glucose	No standardised treatment protocol Limited data collection
Jacob et al[16]	2019	Adult admissions via emergency department (USA) (n = 172)	10 units of insulin with 25g dextrose	19.8% (34/172 patients)	Lower pre-treatment glucose	Did not distinguish type of DM

					Higher pre-treatment potassium	
Schafers et al[8]	2012	Adult inpatients (USA) (n = 219)	Variable dose of both insulin and glucose	8.7% (19/219 patients)	Low body weight	No standardised treatment protocol No/minimal statistical analysis Did not distinguish type of DM
Scott et al[15]	2019	Adult admissions via emergency department (USA) (n = 409)	Variable dose of both insulin and dextrose	16.6% (68/409 patients)	Lower pre-treatment glucose Higher insulin dose Lower dose of dextrose	No standardised treatment protocol Did not distinguish type of DM

Table 3. Previous studies investigating iatrogenic hypoglycaemia following GwI infusions



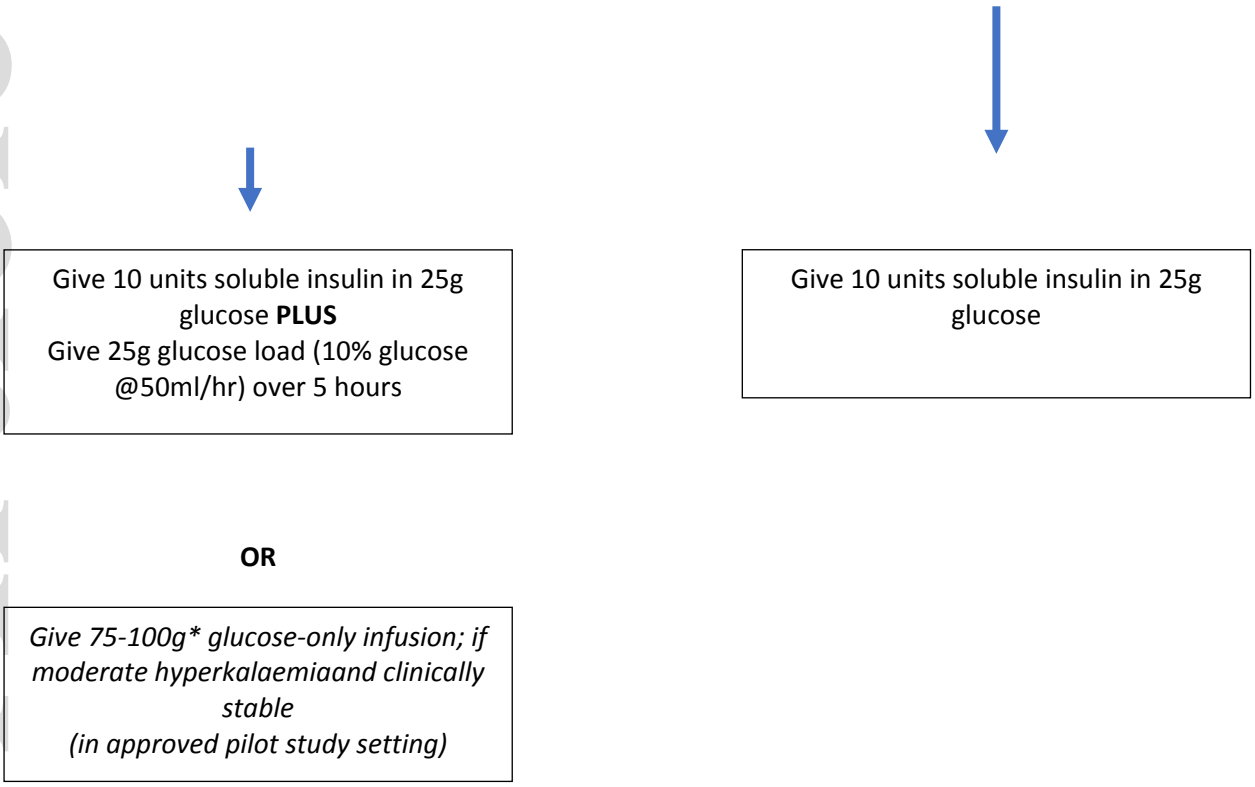


Figure 3. Proposed changes to glucose-insulin infusion treatment section in UK Renal Association Hyperkalaemia guideline

** optimum dose to be determined by further study*