PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	**Phase II study of tight glycaemic control in COPD patients with exacerbations admitted to the acute medical unit**
AUTHORS	Archer, John; Misra, Shivani; Simmgen, Marcus; Jones, Paul; Baker, Emma

VERSION 1 - REVIEW

REVIEWER	***Dr Rob Shulman*** Lead Pharmacist - Critical Care Pharmacy Department University College Hospital University College London Hospitals NHS Foundation Trust 235 Euston Road London NW1 2BU
REVIEW RETURNED	13-Jun-2011

THE STUDY	In terms of design the objective was to determine the safety, feasibility and efficacy of TGC. My problems with this are that with a nursing staffing ration of 6:1 patients, the feasibility of use in this setting has not really been tested because as the authors state - that the protocol was followed due to the presence of a dedicated trialist clinician; so it does not adress use in the real world, that is suggested aim in the objective. They summarise in the discussion that TGC was 'feasible' in the AMU. I suggest that hourly BG measurements for the infusion period and subsequent dose adjustment adds a significant work for the nursing staff and pain/inconvenience for the patient, for questionable benefit. This was not fully addressed. One aspect of the methods not described is that the protocol of insulin use is not provided. The testing of blood glucose in the trial was capilliary blood method. There are documented problems in reliability in this method that is well documented in the ICU literature (Kanji et al Crit CAre Med 33 804-10 2005). They found that this method was unreliable especially in the hypoglycaemic range and advised not to use it. Since much of the concept of the current study has been adopted from the crit care literature, one is left thinking what evidence there is that this is a reliable and reproducable method in this patient group.
RESULTS & CONCLUSIONS	The message from the trial is ok but the authors rightly highlight that in the critical care field the evidence has moved away from TGC. They state under Article summary that in light of this AMUs should expore alternative strategies for BG control in COPD, somewhat undermining the relevance of their work. If this is not a concept worth pursuing in the AMU, is this study very relevent?

	I would like to see the following results included. Number of BG tests in each phase. Number and % of patients who experienced a severe hypoglycaemic episodes - as this is the main headline safety result in the critical care literature and this result should be compared with the Van den Burghe and NICE-Sugar studies.
GENERAL COMMENTS	I do have concerns that this research shows that TGC can be implemented in an AMU, albeit with a dedicated researcher present. It adds to the burden on staff with many additional BG measurements and adds to the discomfort of the patient. What is missing is any data that this is a worthwhile treatment for these patients. Do they benefit from this? To my way of thinking this is the 1st question to be answered, if they do not then the relevance of this work on practice is limited. Following on from this, if the initial efficacy data is not present in this patient group, then one could argue that this study is less relevent for practitioners (ie it will not change practice) so arguably should be published in a less high profile journal.

REVIEWER	***Steven Lane*** Lecturer in Medical Statistics Department of Biostatistics University of Liverpool I have no competing interests
REVIEW RETURNED	14-Jun-2011

REPORTING & ETHICS	It is not stated whether ethics approval was granted or not.
GENERAL COMMENTS	Did you consider formal hypothesis tests to compare your results with published data presented in table 3? it might give readers better understanding of differences/similarities in the data

VERSION 1 – AUTHOR RESPONSE

Response to comments

From the Managing Editor, BMJ Open
Please confirm (if this is the case) in the contributorship statement that all authors approved the final submitted version.
All authors approved the final submitted version of the manuscript. This has been added under the contributorship statement p 25

Reviewer: Dr Rob Shulman
In terms of design the objective was to determine the safety, feasibility and efficacy of TGC. My problems with this are that with a nursing staffing ration of 6:1 patients, the feasibility of use in this setting has not really been tested because as the authors state - that the protocol was followed due to the presence of a dedicated trialist clinician; so it does not address use in the real world, that is suggested aim in the objective. They summarise in the discussion that TGC was 'feasible' in the AMU. I suggest that hourly BG measurements for the infusion period and subsequent dose adjustment adds a significant work for the nursing staff and pain/inconvenience for the patient, for questionable benefit. This was not fully addressed.

A trial physician was on the wards for patient set up and was available Mon to Fri 9-5pm. Outside these hours ward nurses did all the work but telephone support was available. Their excellent protocol adherence (p 20) indicates that they were able to do this as part of their workload. We were

concerned about potential patient discomfort, but only 2 out of 14 who completed an acceptability questionnaire were unhappy with the number of finger pricks required and most patients found the study acceptable and would have been prepared to go through the same procedures again (p 21).

One aspect of the methods not described is that the protocol of insulin use is not provided.
We have now uploaded our protocol and recording sheets as supplementary data

The testing of blood glucose in the trial was capillary blood method. There are documented problems in reliability in this method that is well documented in the ICU literature (Kanji et al Crit CAre Med 33 804-10 2005). They found that this method was unreliable especially in the hypoglycaemic range and advised not to use it. Since much of the concept of the current study has been adopted from the critical care literature, one is left thinking what evidence there is that this is a reliable and reproducible method in this patient group.
We acknowledge that capillary glucose can underestimate hypoglycaemia in critical illness. However capillary blood is widely used for blood glucose monitoring on hospital wards in diabetic patients on insulin, including those on sliding scales and those admitted with hypoglycaemia. Arterial blood glucose monitoring is not possible in patients on acute wards as arterial lines cannot be inserted in this setting. It is possible that we underestimated hypoglycaemia in this study and have made a statement to this effect in the discussion (p22, reference 23). However as our conclusion is that the risk of hypoglycaemia from tight glycaemic control is at least as great in acute wards as it is on intensive care, this doesn't alter our overall message, that alternative strategies should be explored. The last sentences of our abstract (p2) and discussion (p 24) have been altered to strengthen this conclusion.

The message from the trial is ok but the authors rightly highlight that in the critical care field the evidence has moved away from TGC. They state under Article summary that in light of this AMUs should expore alternative strategies for BG control in COPD, somewhat undermining the relevance of their work. If this is not a concept worth pursuing in the AMU, is this study very relevent?

This work is part of a larger programme towards improving outcomes for COPD exacerbations. This programme has:

1. Shown an association between acute hyperglycaemia and poor outcomes in COPD [1]
2. Identified mechanisms whereby acute hyperglycaemia could drive poor outcomes in COPD [2,3,4]
3. Established that insulin has anti-inflammatory actions in COPD4
4. Tested the safety and tolerability of insulin in the acute situation for COPD patients (this study, ISRCTN 42412334, UKCLRN 5689).
5. Identified metformin as a preferable alternative to insulin for blood glucose control in acute exacerbations and shown in a retrospective study that COPD patients taking metformin had longer survival following hospitalisation for exacerbation than those without (submitted to Thorax 2011, outcome awaited)
6. Commenced a randomised, placebo controlled trial to determine the tolerability, safety and efficacy of metformin for acute COPD exacerbations, funded by the British Lung Foundation and adopted by the NIHR portfolio (UKCLRN 10063, ISRCTN 66148745)

The study described in this paper is a key step in this research programme. We demonstrated that we could perform tight glycaemic control in patients with COPD exacerbations with similar safety and efficacy to that achieved on ICU. However just as we completed the study, NICE Sugar was published which showed increased mortality in patients undergoing tight glycaemic control with insulin on ICU. We therefore looked for an alternative strategy for glycaemic control in COPD. Although we do not plan to take the insulin work forward, we feel that it should be published as it provides information about glycaemic control in COPD patients on steroids, as well as around feasibility and acceptability

of clinical trials in acutely unwell inpatients.

1. Baker EH, Janaway CH, Philips BJ, Brennan AL, Baines DL, Wood DM, Jones PW. Hyperglycaemia is associated with poor outcomes in people admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. Thorax 2006; 61:284-289.
2. Baker EH, Clark N, Brennan AL, Fisher DA, Gyi KM, Hodson ME, Baines DL, Philips BJ, Wood DM. Hyperglycaemia and cystic fibrosis alter respiratory fluid glucose concentrations estimated by breath condensate analysis. J Appl Physiol 2007; 102:1969-75.
3. Brennan AL, Gyi KM, Wood DM, Johnson J, Holliman R, Baines DL, Philips BJ, Geddes DM, Hodson ME, Baker EH. Airway glucose concentrations and effect on growth of respiratory pathogens in cystic fibrosis. J Cyst Fibros. 2007; 6:101-109
4. Archer JRH, Wells CE, Hitchings AW, Dodd JW, Herrera C, Baker EH. Systemic inflammation is enhanced by acute hyperglycaemia and suppressed by insulin in COPD. Eur Resp J (abstract) 2011: In Press

I would like to see the following results included.
Number of BG tests in each phase.
On page 15 this has been added to table 2 (IV 617, SC 494)

Number and % of patients who experienced a severe hypoglycaemic episodes - as this is the main headline safety result in the critical care literature and this result should be compared with the Van den Burghe and NICE-Sugar studies.
2 patients each had one episode where capillary glucose was <2.2mM. In the Van den Berghe and NICE Sugar studies, 5% and 6.8% patients respectively on intensive insulin therapy experienced severe hypoglycaemia. We have now added this statement to results (p19) and added NICE sugar as reference 20.

I do have concerns that this research shows that TGC can be implemented in an AMU, albeit with a dedicated researcher present. It adds to the burden on staff with many additional BG measurements and adds to the discomfort of the patient. What is missing is any data that this is a worthwhile treatment for these patients. Do they benefit from this? To my way of thinking this is the 1st question to be answered, if they do not then the relevance of this work on practice is limited. Following on from this, if the initial efficacy data is not present in this patient group, then one could argue that this study is less relevent for practitioners (ie it will not change practice) so arguably should be published in a less high profile journal.
These points have been addressed above

Reviewer: Steven Lane

It is not stated whether ethics approval was granted or not.
This is stated in the first paragraph of methods, page 6

Did you consider formal hypothesis tests to compare your results with published data
We considered doing this using a metaanalysis type approach. However due to relatively small numbers both of comparator studies and of patients in our study and differences in study design we felt that formal hypothesis testing would not add much to the visual presentation of the data.

VERSION 2 - REVIEW

REVIEWER	***Rob Shulman***
REVIEW RETURNED	21-Jun-2011

THE STUDY	I would ask the authors to look again at the incidence of hypoglcaemia that they compare in the literature. The key study below in medical patients (so broadly similar to their cohort) reported an incidense of severe hypoglycaemia of 18.7% of patients in the TGC group; The authors quote the incidense from the van den bergue surgical study which is less relevent. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med 2006;354:449-61.

VERSION 2 – AUTHOR RESPONSE

Many thanks for your email
In response to Dr Shulman's remaining comment above we have amended our statement on page 19 to reference the medical ICU study rather than the surgical ICU study as per the attached document

The statement now reads
2 (10%) patients each had one episode where capillary glucose was <2.2mM. In single centre [20] and multicentre [21] intensive insulin trials, 18.7% and 6.8% patients respectively on intensive insulin therapy experienced severe hypoglycaemia.

Many thanks for your consideration
BW
Emma Baker
On behalf of the authors

The new reference is
20. Van den Berghe G, Wilmer A, Hermans G et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354:449-61.