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Effect of intensive glycaemic control on moderate hypoglycaemia and ICU length of stay in severe traumatic brain injury

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See related research by Hermanides et al. https://ccforum.biomedcentral.com/articles/10.1186/s13054-017-1883-y

Glycaemic alterations are prevalent and modifiable secondary insults with detrimental consequences in neurocritically ill patients. Without discerning whether hyperglycaemia is a marker of lesional severity or the cause of brain damage, its association with poor results is clear due to its deleterious effects by promoting inflammation, thrombosis of the microcirculation and immunosuppression, among others. On the other hand, both the duration and depth of an episode of hypoglycaemia have a negative influence on final outcome. Despite this, a general consensus regarding the best glycaemic control in traumatic brain injury (TBI) has not been established yet.

We read with great interest the article "Glycaemic control targets after traumatic brain injury: a systematic review and meta-analysis" by Hermanides et al. [1]. Although the authors attempted to summarize the best evidence possible, we want to discuss some issues that may render their conclusions controversial. First, the authors did not perform sensitivity analysis to evaluate the effect of specific studies on the results, undoubtedly leading to wrong interpretations, thus limiting the validity of their study.

Second, after analyzing the data from the included studies and performing a sensitivity analysis using the leave-one-out method in Stata v.13, we found that a single study (Bilotta et al. [2]) was influencing the pooled effect size for the risk of moderate hypoglycaemia (blood glucose (BG) < 80 mg/dL) (Table 1), which the authors reported as non-significant in the first place (relative risk (RR) = 0.26; 95% confidence interval (CI) [0.00, 27.84], $P = 0.57$). By removing the study by Bilotta et al., the risk of moderate hypoglycaemia is higher with intensive glycaemic control (RR = 0.15; 95% CI [0.10, 0.23], $P < 0.01$). This is relevant because intensive glycaemic control has been associated with moderate and severe hypoglycaemia, which have been associated with poor outcomes.

Third, the included studies [2–5] consistently reported the ICU length of stay as a clinical outcome. The pooled effect size for this outcome was not estimated in the study. We found that there was no significant difference between intensive versus conventional glycaemic control with regard to ICU length of stay (standardized mean difference = – 0.08; 95% CI [– 0.28, 0.11], $P = 0.39$) (Fig. 1).

Finally, we have two simple questions. Microdialysis studies have revealed that lowering levels of glycaemia below 110 mg/dL is associated with the development of metabolic crises in a brain vulnerable to glucose deficit; therefore, should the definitions of hypoglycaemia not be reconsidered in this context? And is the dichotomized Glasgow Outcome Scale a good form to evaluate the final outcome in severe TBI?

Authors' response

J. Hermanides, M. P. Plummer, M. Finnis, A. M. Deane, J. P. Coles and D. K. Menon

We thank Rafael Núñez-Patiño and coworkers for their interest and comments on our article [1], to which we would like to respond. The authors have suggested the results lack validity as we did not perform a sensitivity analysis to evaluate the effect of specific studies. They have supported this assertion by performing a leave-one-out analysis—identifying one outlier study for the secondary outcome 'moderate hypoglycaemia'—which results in a

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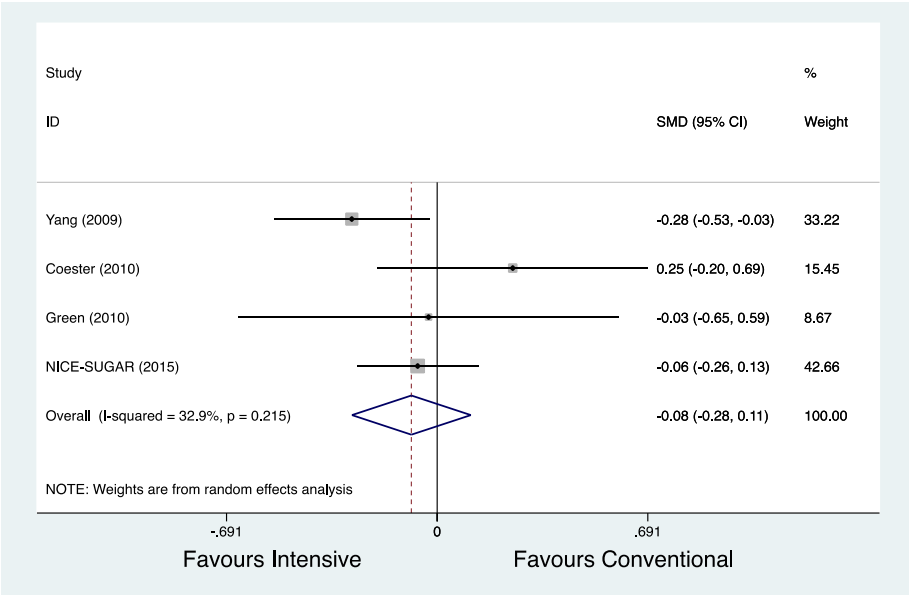
Table 1 Sensitivity analysis comparing the risk of moderate hypoglycaemia (BG < 80 mg/dL) with intensive versus conventional glycaemic control

Study omitted	Year	RR	95% CI	*P* value	Heterogeneity (I^2)	*P* for heterogeneity
Bilotta et al. [2]	2008	0.15	0.10, 0.23	< 0.01	11%	0.34
Coester et al. [3]	2010	0.27	0.00, 96.34	0.67	100%	< 0.01
Green et al. [4]	2010	0.27	0.00, 66.88	0.64	100%	< 0.01
NICE-Sugar [5]	2015	0.33	0.01, 12.31	0.54	99%	< 0.01
Van den Berghe [6]	2005	0.27	0.00, 50.32	0.63	100%	< 0.01
Combined [2–6]		0.26	0.00, 27.84	0.57	100%	< 0.01

BG blood glucose, *CI* confidence interval, *RR* relative risk

statistically significant association between moderate hypoglycaemia and intensive insulin therapy, in keeping with the association reported for our primary outcome, severe hypoglycaemia.

Given their analysis, we assume they have also confirmed that there are no outlier studies for the primary outcomes, i.e., mortality and severe hypoglycaemia. The presence of marked heterogeneity for the 'moderate hypoglycaemia' studies was clearly recognized and reported in our paper ($I^2 > 95\%$), with the influence of the Bilotta study clearly shown in the forest plot (Fig. 6 in [1]). We chose to analyse the data with a random effects model as it was clear from looking at the heterogeneity within patient populations, glycaemic control protocols and metrics of glycaemic control that we would not be estimating a common treatment effect, but rather the range of effects present in relevant studies. In keeping with Higgins, we do not believe heterogeneity allows removal of an offending study. To quote him, this approach "raises important questions about the validity of the subsequent meta-analysis, since removal of studies is tantamount to manipulation of the eligibility criteria" [6]. We believe reporting all relevant studies, along with heterogeneity, is a more valid approach, as this presents the reader with all relevant information, allowing the type of post-hoc subset analysis performed by Núñez-Patiño et al.



Abbreviations:

SMD: Standardized mean difference

95%CI: 95% confidence interval

Fig. 1 Forest plot comparing ICU length of stay in days between intensive versus conventional glycaemic control

Notwithstanding, these issues do not meaningfully alter the interpretation of our paper, as this post-hoc analysis of a secondary outcome parallels the findings of our primary outcome, i.e. both moderate and severe hypoglycaemia are associated with intensive insulin therapy [7].

Second, we thank Núñez-Patiño for performing a meta-analysis on length of stay for the different studies. We did not include this as an endpoint in our paper because ICU length of stay is not a patient-centred outcome and can be manipulated by many factors, including competing risk of death. The interpretation thus warrants caution.

Finally, we agree with Núñez-Patiño et al. that microdialysis glucose levels may be important, but we need to recognize that they do not address the risks of hyperglycaemia either cerebrally or extracranially. We have to be aware that ICU research is littered with interventions that made the numbers better but the patients worse.

To conclude, we agree that any meta-analysis should be interpreted with caution, especially in cases of marked heterogeneity. However, excluding studies from meta-analysis should be done based on predefined inclusion and exclusion criteria, and not because we do not 'like' the results.

Availability of data and materials

Data supporting our findings can be found in the references of this manuscript and the randomized controlled trials which assessed the impact of intensive versus conventional glycaemic control in patients who suffered from traumatic brain injury; this information was published in each article.

Authors' contributions

RANP contributed to the definition of intellectual content, literature search, data acquisition, data analysis, manuscript editing, manuscript preparation and manuscript review and submitted the article to the journal. AZV contributed to the literature search, data analysis, manuscript editing and manuscript preparation. DAG contributed to the definition of intellectual content, literature search, manuscript editing and manuscript preparation. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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