Clinical study

Dynamic cerebral autoregulation during early orthostatic exercise in patients with severe traumatic brain injury: Further exploratory analyses from a randomized clinical feasibility trial

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Contents lists available at ScienceDirect
Journal of Clinical Neuroscience
journal homepage: www.elsevier.com/locate/jocn

ARTICLE INFO

Article history:
Received 16 April 2021
Accepted 25 July 2021

Keywords:
Dynamic cerebral autoregulation
Early mobilization
Head-up tilt test
Orthostatic intolerance
Traumatic brain injury

ABSTRACT

In patients with severe traumatic brain injury, there is limited evidence of the clinical effect of early orthostatic exercise, although such exercise may strengthen systemic or cerebral hemodynamic responses to head-up tilt, thereby minimizing orthostatic intolerance. We measured dynamic cerebral autoregulation (dCA) and the occurrence of orthostatic intolerance after four weeks of regular orthostatic exercise by head-up tilt using a tilt table with integrated stepping using the ERIGO® tilt-table and comparing it to standard care. Thirty-four patients with severe traumatic brain injury admitted to a neurocritical care unit were included in this randomized clinical trial. Middle cerebral artery blood flow velocity (MCAv), non-invasive mean arterial pressure, heart rate and PaCO2 were recorded; dCA was measured by the non-invasive mean flow index (nMxa). Transition from the supine position to head-up tilt triggered a 10–16% decrease in MCAv and increased nMxa in both groups at all time points (P < 0.05), with no differences between groups. There was no difference in the number of episodes with orthostatic intolerance (5 vs 3; 1 vs 2; 1 vs 0) at baseline, two weeks and four weeks, respectively, and no association between changes in PaCO2-adjusted nMxa and the occurrence of orthostatic reactions (P = 0.35). Early orthostatic exercise does not affect dynamic cerebral autoregulation and does not protect against orthostatic intolerance in patients with severe traumatic brain injury. Trial registration: ClinicalTrials.gov identifier: NCT02924649. Registered on 3rd October 2016.

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1. Introduction

Recent studies report that early mobilization may have beneficial effects on functional outcomes in critically ill patients [1]; however, the effects are less well studied in patients with traumatic brain injury (TBI) [2,3]. Many patients with TBI, particularly those with severe injuries, require prolonged deep sedation to treat intracranial pressure increases and cerebral metabolic crisis [4]. The accompanying immobilization may lead to orthostatic intolerance [5] due to haemodynamic decompensation and changes in autonomic regulation [6], which may subsequently manifest as orthostatic intolerance during mobilization to the upright position [7,8]. Conversely, regular mobilization on a tilt table, here designated ‘orthostatic exercise’, has previously been reported to restore orthostatic tolerance in patients with neurally mediated syncope, which may both involve beneficial effects on systemic vascular tone, fluid retention, and dynamic cerebral autoregulation (dCA) [9]. It remains to be determined whether this is also the case in patients with severe TBI.

https://doi.org/10.1016/j.jocn.2021.07.047
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The aim of this study was to investigate the effects of orthostatic exercise on systemic and cerebral haemodynamics in a population of patients with severe TBI. The patients were studied as part of a randomized feasibility trial investigating the feasibility and safety of orthostatic exercise [10].

2. Methods

The study was based on measurements collected during a randomized feasibility trial [10] which was conducted following the latest version of the Helsinki Declaration [11] and the ICMJE Recommendations for the Protection of Research Participants (www.icmje.org). The study protocol was published [12], approved by the Scientific-Ethics Committee of the Capital Region in Denmark (H-16041794), and registered at ClinicalTrials.gov (NCT02924649).

2.1. Participants

Thirty-eight patients were included within 12.8 (SD 5.2) days (time of first autoregulation assessment) after admission with severe TBI to an acute neurointensive care unit [10] (Supplemental Table 1). Inclusion criteria were Glasgow Coma Score (GCS) <11, suspected persisting disorder of consciousness (unresponsive wakefulness syndrome or minimally consciousness state), and a suspected persisting disorder of consciousness (unresponsive wakefulness syndrome or minimally consciousness state), and a stable intracranial pressure (<20 mmHg) during the past 24 h. Exclusion criteria were fractures of the lower extremities that prohibited weight-bearing, spinal cord injury, or lack of informed consent from the next of kin.

2.2. Randomization and masking

Patients were randomly assigned (1:1) to either early orthostatic exercise (intervention group) or standard care (control), using a web-based computer-generated block-randomization procedure. Block sizes were randomly assigned as either 4, 6, or 8 patients in each block. We stratified the randomization according to either low or high GCS (3–6 and 7–10, respectively). Due to the nature of the intervention (tilt-table), it was not possible to mask the intervention to the clinical staff or the patient.

2.3. Orthostatic intolerance

According to the trial protocol [12], orthostatic intolerance was defined as “relative” when blood pressure dropped more than 30 mmHg systolic or 15 mmHg diastolic or heart rate increased by more than 30 bpm from supine values during head-up tilt, and as “absolute” in case of a reduction of blood pressure to 80 mmHg systolic or 50 mmHg diastolic or an increase in heart rate to 180 bpm. This was assessed during the orthostatic exercises by the treating staff, who returned the patient to the supine position if any of the above limits were surpassed.

2.4. Intervention and standard care

The early orthostatic exercise consisted of daily (weekdays) head-up tilt on an ERIGO® tilt-table (Hocoma, Switzerland) to 70 degrees tilt for 20 min. In case of a critical reduction in either blood pressure or cerebral perfusion pressure, or an increase in intracranial pressure or heart rate as described above, the patient was moved to 0 degrees until stable and then returned to standing [12]. Time at 0 degrees was not considered part of the 20-minute session. Patients who regained the ability to stand up during the four-week intervention period did not undergo further orthostatic exercise, but remained in the study.

Treatment in the standard care group was decided by the treating physician, nurses, and therapists. Mobilization could be a part of the standard care but occurred at a much smaller scale than in the intervention group; the major focus of standard care was respiratory optimization and re-positioning to prevent pressure ulcers. As previously reported [10] the standard care group did not receive orthostatic exercises, but they did undergo alternative types of mobilisations more frequently (median 8 times – interquartile range 3–16) than the early orthostatic exercise group (median 3 – interquartile range 0–9) during the four-week intervention period.

2.5. Measurements

At baseline, two and four weeks follow-up, a 5-minute head-up tilt was performed in both groups using the same tilt table as described above. During tests, continuous non-invasive arterial blood pressure was measured using a photoplethysmograph on the middle index finger at heart level (ADInstruments, Oxford, UK), while heart rate was measured from three-lead ECG. Transcranial Doppler ultrasound was used to measure unilateral linear middle cerebral artery blood flow velocity (MCAv) by the continuous measurement of backscattered Doppler signals using a 2-MHz pulsed transcranial Doppler (TCD) ultrasound system (Multi-Dop® T digital, Compumedics Germany GmbH, Singen, Germany). Following a standardized search technique [13], the Doppler probe was secured over the transtemporal window with an adjustable metal LAM rack (Compumedics Germany GmbH, Singen, Germany) and an insonation depth for MCAv of 45–60 mm. Arterial blood samples were obtained from the radial artery contralaterally to the plethysmography, both in the supine position and at the end of the head-up tilt, and were immediately analyzed on a nearby arterial blood gas analyzer (ABL800, Radiometer, Copenhagen, Denmark).

2.6. Data analysis

Data in the supine position and during head-up tilt was visually inspected using Labchart reader (ADInstruments, Oxford, UK). Two data files, containing periods of artefacts in the continuous blood pressure and Doppler signals were generated alongside the visual inspection and were analyzed using an R-script (R version 3.6.1, R Core Team, Vienna, Austria) [14]. Quality control of the data was done through the R-script and presented in Supplemental Table 2. The following indices were calculated: the non-invasive mean flow index (nMxa), the cerebrovascular resistance index (CVR), and the Gosling’s Pulsatility index (GPI).

2.7. Statistical analyses

As stated in the trial protocol [12], the statistical analysis plan for the present explorative analysis was prepared before the data was analysed [15]. However, due to an unexpected amount of missing data, we were unable to comply entirely with the original plan.

Briefly, the nMxa was used as a continuous variable for analyzing the patient’s dCA. Firstly, we compared the nMxa after four weeks for between-group differences using a mixed-effects model. Secondly, the mixed-effects model was used to investigate differences over time and between groups for the nMxa and each of the other hemodynamic variables. Thirdly, a mixed-effects model was used to investigate the association between the nMxa and orthostatic intolerance, as we applied the latter to the model. The difference in the occurrence of orthostatic intolerance between groups was calculated using Fisher’s exact test.
Lastly, the power of the primary outcome for comparisons between two (unpaired groups) was calculated using a two-sample t-test power calculation, and the concomitant effect-size was then estimated at four weeks using Hedges’ g.

All statistical analyses and graphical presentations were done using SAS/STAT software (SAS Institute Inc., Cary, NC, USA) and R (version 3.6.1, R Core Team, Vienna, Austria).

3. Results

Of 38 patients included in the feasibility study (19 in each group), 34 patients (17 in each group) underwent a head-up tilt test at baseline. Two patients had poor insonation windows, one measurement was of poor quality, and equipment malfunction occurred in one patient. For analysis between groups, 16 patients underwent head-up tilt at four weeks (9 in early orthostatic exercise, 7 in the standard care). Four patients died during the study period and could, therefore, not be re-tested at four-weeks (Fig. 1).

During head-up tilt, MAP and HR showed a small but insignificant increase at all time points in both groups (Fig. 2). Although supine MAP was lower at baseline in the early orthostatic exercise group compared to the control group, the MAP responses did not differ between groups at 2- and 4-week follow-up. HR also increased during head-up tilt in both groups at all time points. MCAv decreased during head-up tilt in both groups at all time points, with a concomitant increase in CVR (Fig. 3); no differences were observed between groups. Arterial blood gas values also did not differ between groups (Supplemental Table 5).

During the head-up tilt at baseline 5 out of 18 patients in the early orthostatic exercise group vs 3 out of 17 patients in the standard care group experienced orthostatic intolerance. This number decreased at two weeks (1/9 vs 2/9) and four weeks (1/10 vs 0/7) (Supplemental Table 3).

The nMxa increased from supine to head-up tilt (P < 0.05) at all time points with no difference between groups; the only exception occurred at two weeks, where nMxa decreased from supine to head-up tilt in the standard care group (P < 0.05) (Fig. 3). The increase in nMxa was not associated with orthostatic intolerance when adjusting for PaCO2; in contrast, the mixed-effects model estimated a decrease in nMxa of –0.048 when orthostatic intolerance was present (Supplemental Table 3 and 4). The calculated effect-size for nMxa at four weeks was low and estimated at 0.11 (Hedges’ g). The sample size required to detect a similar difference between two groups was estimated at 2240 patients.

4. Discussion

In the current study, we found no evidence to suggest that early orthostatic exercise compared to standard care affected dCA in patients with severe TBI, neither in the supine nor in the head-up tilt position. A quarter of all patients experienced orthostatic intolerance, more so in the early phase; however, this was not associated with impaired dCA.

Our results suggest that early orthostatic exercise is safe in patients with severe TBI, at least in those with stable intracranial pressure. The patients did experience a drop in MCAv during head-up tilt, at the same magnitude as that observed in healthy males (12% in the present study vs 9 % in healthy volunteers at 60 degrees tilt) [16]. Head-up tilt was associated with a slightly less effective dCA, consistent with the changes observed during
head-up tilt in healthy volunteers when lower body negative pressure was simultaneously applied to challenge normal cardiovascular regulation [17]. The development of orthostatic intolerance was unrelated to changes in PaCO₂-adjusted dCA. Hence, our findings do not support the contention that orthostatic intolerance in these patients is related to changes in dCA. On the other hand, patients were moved to the supine position as soon as our predetermined limits were crossed, which in part could explain why the Mxa did not increase further.

Data sampling was affected in particular by patients who were lost to follow-up but also due to poor quality data in some of the recordings. It is not uncommon for studies using transcranial Doppler ultrasound only to use good quality data, even though this renders the interpretation of data susceptible to bias. These considerations should be taken into account when interpreting the data.

The missing data at follow-up is a clear limitation to this study. Patients were lost for several reasons, notably by transfer to other hospitals when they no longer needed specialized neurosurgical treatment. Apart from the declining sample size, which increased the risk of a type II error, the lack of an effect of early orthostatic exercise on dCA may reflect that the remaining patients represent a subgroup of patients with a poorer prognosis than the patient group as a whole, as we did not follow up on patients who gained the ability to walk. The high GCS strata also showed that the patients in the standard care group had a higher GCS at baseline then the early orthostatic exercise group [10]. Furthermore, patients with short duration of measurements are more likely to have a poor data quality and to be excluded from further analysis. Because short measurements are more likely to occur in patients with orthostatic intolerance, these patients may have had a higher risk of being excluded from dCA analysis.

The small sample size of this trial is illustrated by the calculated effect size and power of the primary outcome, and the results in the present trial should be seen as hypothesis-generating.

In conclusion, early orthostatic exercise does not appear to affect the systemic or cerebral haemodynamic response to head-up tilt in patients with severe TBI. Thus, our findings do not support the hypothesis that early orthostatic exercise protects patients with severe TBI from experiencing orthostatic intolerance. Further research is warranted due to the low power of this trial.

**Author contributions**

CGR, JM, and KM designed the study. CGR collected the data, and CGR and MHO analyzed the data. All authors were involved in the interpretation of the results. CGR drafted the manuscript, and all authors revised it critically. All the authors approved the manuscript.
**Funding**

This work was supported by The Council of Danish Victims Fund, Denmark (grant number 16-910-00043); the Research Fund of Rigshospitalet, Copenhagen University Hospital, Denmark (grant number R114-A4672), and the Danish Physical Therapy Association, Denmark (grant number 15242). The funders did not influence the design of the trial or interpretation of the results.

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Acknowledgements**

We would like to express our gratitude to the staff at the Department of Neuroanaesthesiology, Rigshospitalet, the Intensive Care Unit (Y13) at Glostrup Hospital, Rigshospitalet, and the Department of Neurorehabilitation, TBI unit, Rigshospitalet for their help and willingness in collecting these data.

**Data availability**

All data generated or analysed during this study are included in this published article (and its Supplemental files).

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2021.07.047.

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