Studies on delirium and associated cognitive and functional decline in older surgical patients

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Chapter 8

Summary

Delirium is a neuropsychiatric syndrome that is frequently encountered by older hospitalized adults. Although considered a reversible condition, it is independently associated with important negative outcomes such as a greater risk of institutionalization, dementia, and death. Many delirium episodes that occur in the hospital setting concern surgery patients that experience delirium in the perioperative period. The incidence of perioperative delirium is likely to increase with the aging population and evolving diagnostic and therapeutic procedures that are currently becoming available for a larger number of older patients.

How delirium can result in permanent functional and cognitive impairment in some older patients, is incompletely understood. Also, clinicians who take care of older surgery patients, are often faced with clinical dilemma's concerning the performance of interventions that might prevent or evoke delirium. Lastly, selecting patients on forehand who will improve from surgery on outcomes that are most relevant to older patients like functional independency and quality of life, remains a challenge. Further studying these patient-centered outcomes could improve this process. The aim of this thesis was to shed light on relations observed between perioperative delirium and cognitive and functional decline, in order to improve care and outcomes for older surgery patients.

Part 1: Studies on factors that show a temporal relation with the development of delirium in the perioperative period

In this part we investigated two events that might show a temporal relation with the onset of delirium. We explored the hypothesis that acute irreversible brain damage occurs during an episode of delirium, as an explanation of the association between delirium and subsequent development of cognitive decline. We did so by studying a well-established biomarker of acute brain cell damage, S100B. Next, we investigated whether a blood transfusion can serve as a protecting or precipitating factor for delirium in hip fracture patients with anemia in the postoperative period.

In **chapter 2** we measured the level of S100B in cerebrospinal fluid (CSF) in a sample of hip fracture patients with and without perioperative delirium, who received surgical repair that was performed under spinal anaesthesia. We found no difference in S100B levels between groups. We did find that two patients that were already delirious at the time the CSF sample was taken, had relatively high S100B levels compared to patients who developed delirium after the sample

was taken and compared to patients that did not develop delirium at all. From this we learned that timing of S100B measurement in relation to the onset of delirium seems of major importance when studying the position of this biomarker in research on delirium pathophysiology.

In **chapter 3** we studied S100B in repeated serum samples in a different cohort of hip fracture patients, and the association of S100B level with delirium and cognitive decline after 12 months. We hypothesized that if S100B would be a biomarker of acute brain damage related to delirium, this might reflect in long term irreversible cognitive decline or death. By using repeated S100B measurements we sought to better capture a possible rise in S100B level before, during or after delirium. In this cohort premorbid cognitive impairment was present in 58.7% of patients and 33.0% experienced delirium. Delirium was not associated with higher S100B levels before, during or after delirium, after controlling for important confounders. We found that S100B levels were more often increased in older age, in the presence of an intercurrent infection, and after surgery as compared to levels before surgery. Cognitive decline or death were more often experienced by patients with perioperative delirium than by patients without delirium (58.6% versus 36.5%). To our surprise, higher S100B levels were associated with this outcome only in patients without delirium. A possible explanation is that enough brain tissue might need to be preserved to be able to shed S100B from astrocytes that are damaged. Patients with delirium more often had (advanced) cognitive impairment, and they might have less brain tissue 'to lose'. Based on these results, we were not able to either reject nor confirm the hypothesis of acute brain damage occurring during delirium.

In **chapter 4 and 5** we sought to resolve a clinical dilemma: whether or not to administer a blood transfusion to a post-surgery patient with moderate anemia, but no strict indication for transfusion when following current guidelines. In this scenario blood transfusion could be regarded as a measure to prevent delirium, as it resolves anemia which is a precipitating factor of delirium. On the other hand, transfusion in itself could serve as a precipitating factor due to fact that it is a medical procedure that can result in discomfort, complications and possibly a systemic inflammatory response. In **chapter 4** we provided a systematic literature overview of studies on blood transfusion as a risk factor or protective factor for delirium. We included 23 studies, of whom 21 were observational studies addressing the association of several factors with delirium occurrence, and two were randomized controlled trials (RCT's) investigating different

transfusion strategies and delirium. Quality of the included studies was limited in 22 studies and uncertain in one. Timing of delirium onset with respect to transfusion was a concern, this was only properly addressed in four studies. In one of these studies, it was found that a blood transfusion of >1000 mililiter during surgery was a risk factor for postoperative delirium. In the other three studies no association between transfusion and delirium was found. No proper conclusion could be drawn from the studies that did not describe whether delirium occurred before or after transfusion. Taking this all into consideration, we were not able to solve our clinical dilemma by studying the existing literature.

Therefore, in **chapter 5**, we used our cohort of hip fracture patients, also studied in chapter 3 and 4, to investigate the association of anemia with delirium, and the role of blood transfusion within the multicomponent prevention strategy of delirium. We found that having anemia (hemoglobin level <6mmol/L) at any point during hospitalization was associated with increased odds of experiencing delirium (odds ratio 1.81; 95% confidence interval 1.15-2.86). We next selected a subgroup of patients who had anemia at some point during hospitalization and excluded all patients with delirium onset before administration of transfusion. In this subgroup we found that blood transfusion had an odds ratio of 0.26 (95% confidence interval 0.10-0.70) for development of delirium, which suggest that transfusion might be regarded as a protective factor for delirium in patients with anemia after hip fracture surgery. A limitation of this study was that it was not primary designed to answer our research question, and as the decision to administer a blood transfusion was made by the attending physician, it might be based on factors that not have been accounted for in our analysis.

Part 2: Studies on delirium and its effects on long term functional and cognitive outcome

In part 2 of this thesis, we studied cognitive and functional perfomance of older patients undergoing acute or elective surgery during the first year after the procedure.

In **chapter 6** we described patterns of cognitive change in the first 12 months after surgery in a cohort of hip fracture patients. We were interested in different patterns of improvement and decline that can be seen when no assumptions are made on which predefined subgroups might perform better or worse. We applied an established statistical technique called Group Based Trajectory Modelling (GBTM), using the Mini Mental State Examination (MMSE) as

measurement of cognitive functioning. In the first year after hip fracture, we identified the following three cognitive trajectories: improvement (57.9%), stable (28.1%), and rapid decline (13.9%), with an annual MMSE change of 1.7, 0.8, and -3.5 points respectively. These three groups also showed a clearly distinct clinical phenotype, with age, levels of premorbid cognitive and functional impairment and perioperative delirium rising across worsening trajectory groups. This could be useful information when informing patients and caregivers on possible surgery outcomes, and organizing post hospital care.

Lastly, in **chapter 7**, we studied a cohort of patients undergoing transcatheter aortic valve implantation (TAVI). In this specific population it is known that a proportion of patients does not benefit from the procedure in terms of functional recovery and quality of life. We wanted to explore the role of perioperative delirium as a cause of these negative outcomes. We found that in our cohort the incidence of delirium was 15.4%, and that 38.5% experienced functional decline and 11.0% of patients died during a mean follow up time of seven months. Postoperative delirium resulted in increased odds for the combined outcome functional decline or death. Patients with functional decline reported a lower quality of life than patients with a stable or improved functional status at follow up. These results emphasis that this risk should be incorporated in the process of shared decision making and delirium prevention should remain a top priority in TAVI patients.