Neurally-mediated reflex syncope: diagnosis and treatment
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Chapter 8

Summary of findings
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Transient loss of consciousness (T-LOC) can be caused by various clinical disorders. If T-LOC is caused by transient arterial hypotension and hypoperfusion of the brain due to reflex vasodilatation, bradycardia, or both the disorder is called reflex syncope. Vasovagal syncope (VVS) is the most common cause of reflex syncope. This thesis is about the diagnosis and treatment of reflex syncope, with a focus on VVS.

If patients experiencing T-LOC seek medical attention, attending physicians need to differentiate between the relatively benign and the potentially lethal causes of T-LOC. The clinical history plays a critical role in the initial evaluation of patients presenting with T-LOC as it can provide valuable clues about the underlying cause. It can be difficult to diagnose patients presenting with T-LOC. One reason is that actual episodes of T-LOC are rarely observed by physicians, and an eyewitness’ account of an episode of T-LOC - if present - is not always reliable. Moreover, the signs and symptoms of different causes of T-LOC can be very similar.

In Chapter 2 we hypothesized that not only the incidence but also the clinical features of reflex syncope might differ by age and gender. In order to investigate this, we used data from the Fainting Assessment Study (FAST), a prospective cohort study designed to assess the accuracy of diagnostic strategies for adult patients presenting with T-LOC. In that study, 503 patients (median age 52 years; 56% were men) who presented themselves with T-LOC to one of a number of hospital departments of the Academic Medical Center in Amsterdam were included. Using a structured questionnaire, information about prodromal signs, symptoms and triggers of episodes was collected in a uniform way in all patients. After this evaluation, an initial diagnosis was made and additional tests were performed if necessary. A final diagnosis was made based on all available data after 2 years of follow-up. The FAST-study showed that reflex syncope was overall the most common diagnosis in 60% of patients. We found that reflex syncope was more common in younger patients (73% among patients under 40 years of age) than in older patients (45% among patients aged 60 years or above). The prevalence of all symptoms and signs, except ‘pallor’, was also higher among patients under 60 years of age. Apart from differences in age, the number of episodes of reflex syncope in the last year was higher in women than in men (2 vs. 1; p= 0.02). In general, women reported more prodromal signs and symptoms than men. The fact that signs, symptoms and triggers of reflex syncope are more often reported by women and young people than by men and elderly people can be of value in diagnosing patients presenting with T-LOC.
The Calgary Syncope Symptom Score (Calgary Score) has been developed by the group of Sheldon to select a limited number of items from clinical history that are helpful in distinguishing between VVS and other causes of T-LOC.\(^8\) The Calgary Score consists of seven diagnostic questions. Each positive answer is associated with a number of points. By summing these points a total score is calculated. If patients have a total score equal or above the cut-off value of -2, they are classified as having VVS. Patients with a total score below this cut-off value are classified as not having VVS.

In the study reported in Chapter 3 we evaluated the diagnostic performance of the Calgary Score in the FAST-population. For this purpose, we calculated the Calgary Score for 380 patients presenting with T-LOC. Based on this score, patients were either diagnosed as having VVS or not. The diagnoses based on the Calgary Score were then compared with the final diagnoses, obtained after additional testing and 2 years of follow-up. We found that the sensitivity and specificity of the Calgary Score were 87% (95% CI: 82 to 91%) and 32% (95% CI: 24 to 40%) respectively. In the original study, a sensitivity of 89% and a specificity of 91% had been reported.\(^8\) Though the sensitivity we obtained was similar, the specificity in our validation study was lower. Incorrectly labelling patients as having vasovagal syncope occurred most frequently in patients with psychogenic pseudosyncope (specificity 21%), but was also common in patients with cardiac syncope (specificity 32%). Mortality in patients with cardiac syncope, neurological and unknown causes of T-LOC is higher in comparison to the general population, whereas the prognosis in patients with VVS appears to be benign.\(^4\), \(^9\) The results of our study indicate that the Calgary Score incorrectly labels many patients as having VVS: their actual final diagnoses were different, and potentially more severe. Because of this poor performance in clinical practice, we concluded that the value of the Calgary Score in patients presenting with T-LOC is limited in a general hospital setting.

Non-pharmacological treatment is recommended as the first line of treatment for VVS in current syncope management guidelines.\(^1\) This treatment consists of maintaining an adequate fluid and salt intake, regular exercise and the application of physical counterpressure manoeuvres, like leg crossing, tensing of leg and abdominal muscles and squatting.\(^1\), \(^10\), \(^11\) In relatively mildly affected patients, a combination of lifestyle measures and physical counterpressure manoeuvres has been shown to decrease the syncope burden by 39%.\(^12\) It was unknown whether severely affected patients would benefit from this treatment not only with respect to (pre-)syncopal recurrence but also with respect to another important treatment goal: improving quality of life. In the study reported in Chapter 4 we prospectively evaluated the effectiveness of non-pharmacological treatment in patients that had
experienced at least 3 syncopal recurrences during the last 2 years. In this open study, we recorded syncopal recurrences and quality of life (QoL) in 100 patients receiving non-pharmacological treatment. General QoL was assessed with the Short Form-36 questionnaire; syncope-related QoL was measured with the Syncope Functional Status Questionnaire.

Syncopal recurrence was experienced by 42% of patients within the first 6 months of follow-up, increasing to 49% after one year. Despite these findings, the median number of syncopal recurrences was lower in the first year of non-pharmacological treatment than in the year before treatment initiation (median 0 vs. 3; p< 0.001). In the first year of non-pharmacological treatment, 94% of patients used physical counterpressure manoeuvres. For most of these patients (52%) manoeuvres were beneficial. The most important reasons for failure of this strategy were sudden occurrence of VVS resulting in insufficient time to apply physical counterpressure manoeuvres (56%) and failure of the manoeuvres to stop the process (25%). Four percent of patients had forgotten to apply the counterpressure manoeuvres. In 63% of all patients, we observed both a decrease in syncopal recurrence and an improvement in QoL with non-pharmacological treatment. Since non-pharmacological treatment does have a beneficial effect on both syncopal recurrence and QoL in patients with relatively frequent recurrences of VVS, we recommend that patients diagnosed with VVS, should initially receive non-pharmacological treatment.

A previous study reported that psychiatric symptoms were seen more frequently in VVS patients than in healthy control subjects (71% vs. 23%). We hypothesized that treatment effectiveness might be negatively influenced by the amount of general psychological complaints. We analyzed to what extent the effectiveness of non-pharmacological treatment as described in Chapter 4 was influenced by the extent of general psychological complaints assessed before treatment initiation (Chapter 5). We recorded the prevalence of psychological complaints before the start of non-pharmacological treatment using the Symptom Checklist 90-R (SCL-90-R). This 90-item questionnaire is used to evaluate self-reported general psychological symptoms on a 5-point rating scale. The items of the SCL-90-R are categorized into 9 subscales: agoraphobia, anxiety, depression, somatization, insufficiency of thinking and acting, interpersonal sensitivity and paranoid ideation, hostility, sleep difficulty. The total score, the Global Severity Index, is obtained by summation of all individual subscale scores. The higher the subscale and total scores, the more patients report psychological symptoms. We found that the Global Severity Index before treatment was higher in our patient group than in a reference population (142 vs. 118; p< 0.001). Patients with a 10 points higher Global Severity Index were at increased risk of syncopal recurrence during follow-up (odds ratio 1.11; 95% CI:
1.01 to 1.21). General psychological complaints remained associated with syncopal recurrence(s) after adjusting for other potential prognostic factors such as age, gender and the frequency of syncope during the last 2 years before the start of non-pharmacological treatment. The frequency of syncope during the last 2 years before treatment initiation had the strongest association with syncopal recurrence.

In patients with reflex syncope who fail to respond to non-pharmacological treatment, different kinds of pharmacological or pacemaker treatment might be considered. In the Cochrane Review reported in Chapter 6 we systematically reviewed the literature on the efficacy of different pharmacological treatments: beta-blockers, fludrocortisones, alpha-adrenergic agonists, selective serotonin reuptake inhibitors, ACE inhibitors, disopyramide, anticholinergic agents and salt tablets. We also reviewed evidence on the efficacy of dual chamber pacemaker treatment in patients with VVS, carotid sinus syncope and situational syncope.

We included 40 studies on VVS and 6 on carotid sinus syncope. The criteria for inclusion in our review were not matched by any studies on situational syncope. In total, 2386 patients participated in the 46 included studies. The sample size ranged from 8 to 208 participants, with a median of 42. In many studies head-up tilt testing was used to evaluate treatment effectiveness. The reliability of head-up tilt testing is however low. Provocational tilt testing does not provide information about the ability of interventions to prevent (pre-)syncopal recurrence in daily life. Despite a reasonable number of included trials in our review, many uncertainties remain. The main reasons for this incomplete picture are that studies are small in sample size, use different selection criteria, a variety of control treatments, are often not blinded, and the focus is not always on patient relevant outcomes. Moreover, we decided to analyze the effectiveness of pharmacological treatment independent of the drug dosage in order to be able to draw some conclusions from the limited number of available studies. This could influence the occurrence of syncope and side effects due to dose-effect relationships. In our review, we did not find consistent significant differences for any of the treatment comparisons in our systematic review. We therefore concluded that there is currently insufficient evidence to support the use of any of the pharmacological and pacemaker treatments for VVS and carotid sinus syncope.

In all studies included in our systematic review, treatment was started directly after diagnosis, i.e. without prior non-pharmacological treatment. In the study in Chapter 7 we used a different approach: only patients who experienced a total number of three or more syncopal and/or pre-syncopal recurrences during non-pharmacological treatment (life style measures and physical counterpressure
manoeuvres) received additional randomized, cross-over treatment with midodrine and placebo. Patients received both midodrine and placebo treatment, each for the duration of 3 months, with a one week wash-out period in between. The treatment sequence was determined by a computerized randomization procedure. Patients and the research physician were blinded for the treatment given to the patient. At baseline and after treatment initiation, information was collected about the recurrence of (pre-)syncope, occurrence of side effects and QoL. We analyzed and compared (pre-)syncopal recurrence and QoL between additional treatment with midodrine and placebo.

In this cross-over trial, 23 patients were included (19 were women; mean age 32). The median number of syncopal episodes during treatment was not significantly different for midodrine and placebo treatment (0 vs. 1; \( p = 0.57 \)). We did not observe statistically significant differences with respect to the median number of pre-syncopal episodes (6 vs. 8; \( p = 0.90 \)) and occurrence of side effects during treatment (48\% vs. 57\%; \( p = 0.75 \)). QoL did not differ significantly between midodrine and placebo treatment. We therefore would not recommend prescribing midodrine treatment in patients not responding to non-pharmacological treatment.

This thesis confirms that adequate history-taking is helpful in distinguishing between different causes of T-LOC. In addition to signs, symptoms and triggers, information about age and gender may also contribute, because the distribution of signs and symptoms among patients with reflex syncope differs by age and gender. Our validation study of the Calgary Score shows that any diagnostic tool or pathway developed to diagnose patients presenting with T-LOC should be validated in an external population before implementation in clinical practice.

Our findings indicate that patients severely affected by VVS are likely to benefit from non-pharmacological treatment measures, not only with respect to syncopal recurrence but also quality of life. We therefore recommend that non-pharmacological treatment measures should be offered to all patients diagnosed with VVS.

Based on our systematic review, we conclude there is insufficient evidence to support pharmacological or pacemaker treatment for reflex syncope. However, many of the interventions examined in this review are regularly used in clinical practice. This underlines the importance of designing new trials of good methodological quality and sufficient size to estimate the effectiveness of pharmacological and pacemaker interventions after failure of non-pharmacological treatment. By means of better diagnosis and effective treatment, we may be able to reduce the burden of disease in syncope patients and improve their quality of life.
Reference List