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Expanding the evidence base in the pharmacological management of vasovagal syncope – the next POST

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TITLE Fludrocortisone for the Prevention of Vasovagal Syncope. A Randomized, Placebo-Controlled Trial

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SUMMARY

Syncope is common, with a lifetime prevalence of over 40% and annual incidence of up to 6%.[1,2] At all ages, vasovagal syncope is the most frequent cause of transient loss of consciousness. For the majority of people the condition is self-limiting and does not present to medical attention. It often occurs with an identifiable, and subsequently avoidable, provocative circumstance and is usually a single event. However, in those individuals where syncope recurs, it can become life impacting.

The diagnosis of vasovagal syncope is predominantly clinical, arrived at through a detailed history of the episodes, with no further investigations required. If there is uncertainty about the diagnosis, symptoms are atypical, syncope is recurrent in the absence of heart disease, or is impacting on employment or driving eligibility, head up tilt table testing can help establish a diagnosis.[3]

Surprisingly, given the high prevalence of vasovagal syncope, the evidence base for treatment regimens is sparse or contradictory. The mainstay of management is conservative. A combination of explanation of the mechanism, reassurance, information on avoiding provocative circumstances, good oral fluid intake and actions to take at the onset of prodromal symptoms to minimise the frequency and severity of symptoms are advocated.[4] Physical counterpressure manoeuvres have been demonstrated to significantly reduce syncope recurrence rates.[5]

Despite these measures, a proportion of patients continue to experience disabling symptoms and recurrent syncope. A range of different pharmacological agents have been investigated such as midodrine,[6] beta blockers,[7] selective serotonin re-uptake inhibitors,[8] and fludrocortisone in children,[9] mainly in small scale studies in select populations over short timeframes. The results have been inconclusive.

The multi-centre Prevention of Syncope Trial 2 (POST 2) is the first randomised placebo-controlled trial of fludrocortisone in vasovagal syncope in adults.[10] The investigators recruited patients who had experienced two or more episodes of vasovagal syncope and were symptomatic with Calgary Syncope Symptom Score >=3. Exclusion criteria included hypertension, diabetes mellitus, orthostatic hypotension and previous fludrocortisone use. Subjects were randomised in a double-blind protocol to receive fludrocortisone or placebo with titration of fludrocortisone dose to a maximum of 200 mcg daily. The primary outcome was first recurrence of syncope.

The intended sample size was calculated as 310 patients in order to detect a treatment effect of fludrocortisone equivalent to a clinically relevant relative risk reduction in syncope recurrence of 40%. Despite the high prevalence of vasovagal syncope, only 210 patients were recruited, at a slower than anticipated rate. A reduction in the planned sample size was possible when the combined event rate at interim analysis was higher than anticipated at 50%. Of the sample, 70% were female, median age 30 years (range 21–47). They were a symptomatic population with a median of 15 syncopal episodes in preceding years, and annual syncope frequency of 2.3 events.

Follow-up was for a median of 364 days; 58 patients withdrew from follow-up before syncope, of whom 14 were lost to follow up. For the primary intention-to-treat study outcome, there was a non-significant

reduction in syncopal event rates at 12 months, with 44% recurrence in the fludrocortisone group vs 61% in the placebo arm (hazard ratio (HR) 0.69, 95% confidence interval (CI) 0.46–1.03, p = 0.069). When the analysis was restricted to only include syncope occurring after the first two weeks of treatment, the HR for syncope recurrence improved to a significant 0.62, 95% CI 0.40–0.95, p = 0.029. With post-hoc analysis of only those patients who achieved a stable dose of 200 mcg (61% of intervention subjects), a significant reduction in recurrence of syncope was found (HR 0.51, 95% CI 0.28–0.89, p = 0.019). When a multivariate model was applied to adjust for lifetime syncope occurrence, a significant reduction in syncope in the fludrocortisone group was also reported (HR 0.63, 95% CI 0.42–0.94, p = 0.024).

OPINION

The POST 2 trial provides a modicum of additional evidence to support the use of fludrocortisone as a treatment option for younger patients experiencing recurrent vasovagal syncope. With a smaller than planned population recruited, the investigators were unable to demonstrate the magnitude of risk reduction anticipated. Significant benefit was shown only in post-hoc analyses after up-titration of fludrocortisone dose, with multivariate analysis in more symptomatic subjects, and when syncope occurring during the two weeks of initial treatment was excluded from analysis. It is possible that with a larger study population, or a longer period of stabilisation on fludrocortisone, a significant benefit would have been demonstrated. Subjects recruited were young. Vasovagal syncope has a bimodal presentation, with a second peak incidence in older patients. The trial does not further our knowledge on management in this group, where fludrocortisone has previously been reported as poorly tolerated.[11]

So how should physicians incorporate the findings of this study into clinical practice? In my opinion, the POST 2 trial does support trialling fludrocortisone in the management of vasovagal syncope in younger patients with persistent, life impacting symptoms if there is optimal adherence to non-pharmacological conservative management approaches. There is no evidence for its use in older patients. I recommend obtaining 24-hour ambulatory blood pressure recording prior to therapy, and initiate fludrocortisone in those with lower 24-hour mean blood pressure measurements and not if hypertension is identified. Fludrocortisone should be introduced with caution, particularly in female patients where pregnancy is a possibility. Appropriate counselling about monitoring for hypokalaemia, renal impairment and supine hypertension should be given, along with information on mood disturbance, increased risk of diabetes and infection susceptibility. Sudden cessation of fludrocortisone should be avoided once established on the agent.

I agree with the authors' conclusion that further studies are required to determine if there are particular subgroups of patients who are more likely to respond favourably to fludrocortisone therapy, reflecting the heterogeneity of expression of vasovagal syncope. Gratifyingly, there are current trials examining the effectiveness of other medications. Prevention of Syncope Trial IV is recruiting symptomatic patients with vasovagal syncope to assess whether midodrine is effective at reducing syncope recurrence[12] and POST V is assessing metoprolol in patients over the age of 42 compared with younger patients. In an area of clinical practice with a sparse evidence base, these ongoing studies have the potential to provide greater clarity for clinicians seeking to appropriately manage this common condition in younger patients, but not yet in the older age group.

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