Vitamin B12 for the treatment of recurrent aphthous stomatitis

Abstracted from

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Question: Are sublingual vitamin B12 tablets effective in reducing the frequency of recurrent aphthous stomatitis episodes?

Design This was a randomised, double-blind, placebo-controlled trial.
Intervention One tablet was taken each day before sleep for 6 months. The test group received sublingual vitamin B12 tablets (1000 mcg of vitamin B12) whereas the control group took a placebo of the same shape, size, colour and flavour. Participants met with staff monthly.
Outcome measure Duration (days) of an aphthous stomatitis episode, monthly number of aphthous ulcers, and severity of pain according to the Numerous Rating Scale (NRS), were recorded in a diary.
Results Fifty-eight people suffering from recurrent aphthous stomatitis (RAS) participated: 31 were allocated to the intervention group and 27 to the control group. The duration of outbreaks, the number of ulcers, and the level of pain were reduced significantly ($P < 0.05$) at 5 and 6 months of treatment with vitamin B12, regardless of initial vitamin B12 levels in the blood. During the last month of treatment a significant number of participants in the intervention group reached "no aphthous ulcers status" (74.1% vs 32.0%; $P < 0.01$).
Conclusions Vitamin B12 treatment, which is simple, inexpensive and low-risk, seems to be effective for patients suffering from RAS, regardless of the serum vitamin B12 level.

Commentary

The possible association between recurrent aphthous ulceration (RAU) and vitamin B12 deficiency was first suggested more than 55 years ago.[1] Despite being unsubstantiated because of a lack of robust evidence, it is widely recognised as a possible predisposing factor for RAU. The few available controlled studies analysing haematological status in RAU patients give controversial results, some supporting a link[2,3] whereas others refute a connection.[4,5] Similarly, reports on supplemental treatments are scarce and almost entirely based on studies of doubtful quality that are small in size, uncontrolled, not randomised and unmasked.[6–8]

The present study therefore represents an important advance in this field as it the first randomised, double-blind, placebo-controlled trial on vitamin B12 supplementation in more than half a century. There are, however, a number of subtle yet important problems with it. Firstly, the diagnostic criteria did not consider recurrent intraoral herpetic ulceration, the main differential diagnosis of RAU. Older studies suggested the use of high-dose vitamin B12 in the treatment of herpetic stomatitis, and therefore its absence from the diagnostic criteria is all the more striking.[9] In addition, the vague reporting of clinical details as a possible source of bias does not appear to have been considered. It is unclear whether aphthous ulceration included in the test and control groups was limited to minor RAU or incorporated other varieties. This may be partially explained by the lack of dentists and dermatologists involved in the study.

The authors are also unclear about concealment of allocation sequences, despite assurances that blinding of both physicians and participants occurred until the end of the study. Although patient age, gender and origin were apparently well-matched, educational standard was incompatible between the two groups, with two thirds of the intervention group being highly educated but less than half of the control group fitting this category. There is evidence to suggest a relationship between low income and education, and increased duration and intensity of pain in comparison with higher income/ educational groups.[10] Thus, these differences, although not statistically significant, may have introduced another source of bias. Moreover, no intention to treat analysis was applied, thus an over-optimistic estimate of the efficacy of this intervention is likely because of all the above remarks.

Finally, there is a lack of any consistent biological explanation for the benefits observed, with the authors still suggesting an unrecognised function of vitamin B12. In addition, alternative hypotheses such as *Helicobacter pylori* involvement, a proposed putative aetio-

logical factor of RAU also causing vitamin B12 deficiency[11,12] were not considered.

Regardless of all the criticisms levied, the most outstanding finding of this study is that 74% of individuals in the intervention group were free of ulceration after a 6-month period compared with 32% in the control group. This alone warrants further investigation, through larger and more highly controlled trials, to confirm the effectiveness of vitamin B12 in the treatment of RAU.

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