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Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency

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Abstract

Background—Vitamin B12 deficiency is common and rises with age. Most people with vitamin B12 deficiency are treated in primary care with intramuscular vitamin B12 which is a considerable source of work for health care professionals. Several case control and case series studies have reported equal efficacy of oral administration of vitamin B12 but it is rarely prescribed in this form, other than in Sweden and Canada. Doctors may not be prescribing oral formulations because they are unaware of this option or have concerns regarding effectiveness.

Objectives—To assess the effectiveness of oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency.

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DECLARATIONS OF INTEREST

We have not received any commercial sponsorship for this review.
Dr Andrew McCaddon is a Scientific Consultant for, and shareholder of, COBALZ LIMITED - a private company developing 'glutathionylcobalamin' as an alternative orally available form of vitamin B12.

Search methods—Searches were undertaken of *The Cochrane Library*, MEDLINE, EMBASE and Lilacs. The bibliographies of all relevant papers identified using this strategy were searched. In addition we contacted authors of relevant identified studies and Vitamin B12 research and pharmaceutical companies to enquire about other published or unpublished studies and ongoing trials.

Selection criteria—Randomised controlled trials (RCTs) examining the use of oral or intramuscular vitamin B12 to treat vitamin B12 deficiency.

Data collection and analysis—All abstracts or titles identified by the electronic searches were independently scrutinised by two reviewers. When a difference between reviewers arose, we obtained and reviewed a hard copy of the papers and made decisions by consensus. We obtained a copy of all preselected papers and two researchers independently extracted the data from these studies using piloted data extraction forms. The whole group checked whether inclusion and exclusion criteria were met, and disagreement was decided by consensus. The methodological quality of the included studies was independently assessed by two researchers and disagreements were brought back to the whole group and resolved by consensus.

Main results—Two RCT's comparing oral with intramuscular administration of vitamin B12 met our inclusion criteria. The trials recruited a total of 108 participants and followed up 93 of these from 90 days to four months. High oral doses of B12 (1000 mcg and 2000 mcg) were as effective as intramuscular administration in achieving haematological and neurological responses.

Authors' conclusions—The evidence derived from these limited studies suggests that 2000 mcg doses of oral vitamin B12 daily and 1000 mcg doses initially daily and thereafter weekly and then monthly may be as effective as intramuscular administration in obtaining short term haematological and neurological responses in vitamin B12 deficient patients.

INDEX TERMS: Medical Subject Headings (MeSH)

Administration; Oral; Injections; Intramuscular; Randomized Controlled Trials as Topic; Vitamin B 12 [*administration & dosage]; Vitamin B 12 Deficiency [*drug therapy]; Vitamin B Complex [*administration & dosage]

MeSH check words

Aged; Humans

BACKGROUND

Description of the condition

Vitamins are a group of substances required for effective human metabolism. Under normal circumstances it is essential that they are present in a person's diet because, with few exceptions, the human body is unable to manufacture them. Vitamins often work together with enzymes, co-factors, and other substances. Vitamin B12 (cobalamin) is necessary for the development of red blood cells, growth, and nervous system maintenance. The only dietary sources of vitamin B12 are animal products, such as eggs, fish and meats. Daily

requirements are age-related; the recommended dietary amounts for adults and infants are 1,5 mcg and 0.4 mcg respectively (FAO/WHO 1988, DH 1991).

Vitamin B12 is absorbed in the terminal ileum. This absorption is almost entirely dependent upon intrinsic factor (IF), a glycoprotein secreted by parietal cells situated in the mucosa of the stomach. IF binds to Vitamin B12 and the complex is transported across the cell membrane bound to another glycoprotein called transcobalamin. The most common cause of vitamin B12 deficiency is autoimmune pernicious anaemia, a condition that carries an increased risk of gastric cancer. In pernicious anaemia absorption is impaired due to IF deficiency arising from autoimmune destruction of parietal cells. Other common causes of vitamin B12 deficiency include gastrectomy, ileal resection, pancreatic insufficiency and malabsorption syndromes including Crohn's disease and coeliac disease. Other less common causes include use of drugs such as biguanides (metformin), antacids (proton pump inhibitors and H2 receptors antagonists), aminoglycoside antibiotics, colchicines, and rarely malabsorption due to gastrointestinal bacterial overgrowth and infestation. Pure nutritional deficiency is rare and usually occurs only in strict vegans (EVM 2002).

The true prevalence of vitamin B12 deficiency in the general population is still uncertain but there is evidence that it is common, especially amongst the elderly. The incidence of vitamin B12 deficiency increases with age, probably due to the fact that elderly people are more likely to suffer from food-cobalamin malabsorption. This malabsorption is caused primarily by gastric atrophy but also by chronic carriage of Helicobacter pylori, long term ingestion of metformin and proton pump inhibitors and increased chances of having gastric surgery (Andres 2004). The prevalence of vitamin B12 deficiency in the elderly varies substantially in different studies, largely because of inconsistent diagnostic criteria for vitamin B12 deficiency. Prevalence figures between 1.5% and 15% have been reported (Clarke 2004; Figlin 2003; Pennypacker 1992; Rajan 2002; van Walraven 1999). As well as varying with age, prevalence also varies with gender and ethnic group; elderly men are more likely to have low vitamin B12 levels than elderly women and the prevalence of vitamin B12 deficiency is higher in Europe than in the USA (Lindenbaum 1994; Pennypacker 1992). Vitamin B12 deficiency causes symptoms very similar to folate deficiency: megaloblastic anaemia, chronic tiredness, loss of appetite and mood disturbance. If left untreated, serious neurological and neuropsychiatric complications occur. Vitamin B12 deficiency has also been linked with an increased risk of myocardial infarction and stroke; however this link has not been proved to be causal and it is sustained on the relation between high homocysteine levels and cardiovascular events (Nygard 1997, Carmel 2003). The diagnosis of vitamin B12 deficiency is based mainly on blood measurements of serum vitamin B12, complemented with second lines tests including total homocysteine and methylmalonic acid levels which are metabolic indicators of vitamin B12 deficiency. Studies have indicated that some patients, mainly elderly, can present with neuropsychiatric symptoms in the absence of haematological abnormalities (Lindenbaum 1988).

Description of the intervention

Vitamin B12 (cobalamin) was first isolated in its cyanoform in 1948 (Rickes 1948; Smith 1948), and is now widely used for the treatment of vitamin B12 deficiency. Vitamin B12

replacement has been traditionally administered intramuscularly. However several case control and case series studies have since suggested equal efficacy and safety of the oral route (Chalmers 1958; Ross 1954; Spies 1949). The mechanism for this oral route is most probably that free vitamin B12 can be absorbed both passively (without binding to IF) as well as actively (following binding to IF) in the terminal ileum. Passive diffusion accounts for 1.2% of total absorption with a bioavailability unaffected in patients with pernicious anaemia or gastroduodenal surgical resection (Berlin 1968; Berlin 1978). High doses of oral vitamin B12 (e.g. 1,000 micrograms daily) may be able to produce adequate absorption of vitamin B12 even in the presence of IF deficiency and therefore be an alternative to the intramuscular route in many patients. Despite availability in most countries and a very safe track record, vitamin B12 is rarely prescribed in the oral form. In Sweden, however, in the year 2000, oral vitamin B12 accounted for 73% of the total vitamin B12 prescribed (Norberg 2001; Nilsson 2005). Oral vitamin B12 is also widely used in Canada. Possible reasons for doctors not prescribing oral formulations include unawareness of this option or concerns regarding unpredictable absorption (Lederle 1991; Lederle 1998). In the UK, oral vitamin B12 is not currently available on NHS prescription in high dose formulations.

Most vitamin B12 deficient individuals in the UK and other countries are treated with intramuscular vitamin B12. Intramuscular vitamin B12 can be administered in two different forms: cyanocobalamin and hydroxocobalamin. In some countries hydroxocobalamin has completely replaced cyanocobalamin as first choice for vitamin B12 therapy because it is retained in the body longer and can be administered at intervals of up to three months (BNF 2004). Intramuscular injections are a “considerable source of work” for health care professionals, mainly general practitioners and community nurses (Middleton 1985), and can cause significant pain in thin patients (Elia 1998). While serious adverse reactions are rare, injections can be dangerous in anticoagulated patients. There is little difference in the cost of oral versus intramuscular therapy when the medication alone is considered. However, intramuscular administration often involves a special trip to a health facility or a home visit by a health professional to administer the injection (Lederle 1991). Oral treatment could therefore save considerable Health Service resources.

Archie Cochrane, working in South Wales, was one of the first to identify that substantial financial savings could be made from more evidence-based prescribing of vitamin B12. His focus was on excessive prescription of vitamin B12 (Cochrane 1971). More recently, a Canadian study (van Walraven 2001) has estimated that converting patients aged over 65 years on B12 replacement from the intramuscular to oral form could save between $ 2.9 and $ 17.6 million (2.5 and 15.3 million Euro) over five years in Ontario alone.

Why it is important to do this review

There have been several case control and non-randomised studies assessing the effectiveness of oral vitamin B12 over the last five decades (e.g. Andres 2001; Andres 2003a; Berlin 1968; McIntyre 1960; Spies 1949). We identified a narrative review (Lane 2002) but did not identify any systematic review comparing oral vitamin B12 with intramuscular administration.

OBJECTIVES

To assess the effects of oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency.

METHODS

Criteria for considering studies for this review

Types of studies—Randomised controlled trials examining the use of oral versus intramuscular vitamin B12 to treat vitamin B12 deficiency.

No minimum trial duration or post intervention follow-up restriction.

Exclusions:

- studies examining the role of vitamin B12 in the prevention of cardiovascular diseases, because the dose of vitamin B12 used in those studies may be different from the dose used to treat vitamin B12 deficiency and the majority of patients included in these studies are not vitamin B12 deficient;
- studies of patients with primary folate deficiency, because the concomitant use of folate might confound the metabolic outcome measures;
- studies of patients with end-stage renal disease or on haemodialysis, because renal disease might confound the metabolic outcome measures.

Types of participants—Study participants with low serum vitamin B12 levels, meeting criteria for vitamin B12 replacement therapy. We used a cut-off point of 180 pmol/L (or 240 pg/mL) as threshold serum level for vitamin B12 deficiency. Although there has been some controversy regarding the cut-off point to define vitamin B12 deficiency, values between 120 and 180 pmol/L have been consistently used and 180 pmol/L is a value that ensures a wider inclusion of studies.

Types of interventions—Oral vitamin B12 versus intramuscular vitamin B12.

Types of outcome measures

Primary outcomes

- serum vitamin B12 levels;
- clinical signs and symptoms of vitamin B12 deficiency (e.g.. depression, tiredness, paralysis, dementia).

Secondary outcomes

- haemoglobin and mean corpuscular volume (MCV);
- total homocysteine and serum methylmalonic acid levels;
- costs;
- adverse effects of oral and intramuscular vitamin B12 treatment;

- acceptability to patients;
- quality of life (ideally measured with a validated instrument).

Search methods for identification of studies

Electronic searches—We did not have any language restrictions. We searched the following databases:

- *The Cochrane Library* (Issue 1, 2005), including the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Reviews of Effectiveness (DARE);
- MEDLINE (up to December 2004);
- EMBASE (up to December 2004);
- Lilacs - www.bireme.br (up to December 2004).

To identify ongoing trials we searched:

- The National Research Register (UK) (http://www.update-software.com/national);
- Current Controlled Trials (http://www.controlled-trials.com);
- National Institutes of Health (USA) (http://clinicalstudies.info.nih.gov).

Our search strategy was based on the strategy described in the Cochrane Reviewers' Handbook (Optimal Search Strategy for RCTs. Appendix 5c). The search strategy was used for searches of MEDLINE Ovid Web and adapted for other electronic databases. For the detailed search strategy see Appendix 1.

It was agreed that if during our search we identified any additional key words of relevance, we would adapt our strategy accordingly and re-run the search.

Searching other resources—The bibliographies of all relevant papers identified by this strategy were searched for additional studies.

We contacted (by e-mail or letter) the authors of relevant studies, experts in the field and Vitamin B12 manufacturers to enquire about additional published or unpublished studies, ongoing trials and to obtain additional references.

Data collection and analysis

Selection of studies—All abstracts or titles identified by the electronic searches were independently scrutinised by two researchers (JVA examined all the abstracts and divided the abstracts between CCB, RCJ and KH to provide a second review). When uncertainty arose, or when there were differences between these reviewers, we obtained and reviewed the hard copies of papers and made decisions by consensus.

The whole group checked whether inclusion and exclusion criteria were met and disagreement was resolved by consensus.

Data extraction and management—We obtained a copy of all selected papers. JVA extracted data from all the papers and another researcher (either AMC or RCJ) also extracted data from each paper using piloted data extraction forms.

Assessment of risk of bias in included studies—The methodological quality of the included studies were independently assessed by two researchers (CCB and RCJ) and disagreements brought back to the whole group for discussion.

We used the scheme described in the Cochrane Collaboration Handbook for assessing methodological quality. This scheme uses the criteria specified by Schulz and by Jadad (Jadad 1996; Schulz 1995) and involves assessing studies for:

- publication bias
- selection bias - a) was the randomisation procedure adequate? b) was the allocation concealment adequate?
- performance bias - a) were the patients and people administering the treatment blind to the intervention?
- attrition bias - a) were withdrawals and dropouts completely described? b) was analysis by intention-to-treat?
- detection bias - were outcome assessors adequately blinded to the intervention patients received?

Based on these criteria a 3-point rating scale was used, with the following grading:

A - all quality criteria met: low risk of bias (plausible bias is unlikely to alter the results seriously)

B - one or more of the quality criteria only partly met: moderate risk of bias (plausible bias raises some doubt about the results)

C - one or more criteria not met: high risk of bias (plausible bias seriously weakens confidence in the results)

Data synthesis—We planned to perform meta-analysis if studies were sufficiently similar in terms of inclusion criteria, settings, treatment, follow up assessment and quality. We aimed to evaluate equivalence between the oral and intramuscular routes of vitamin B12 administration. We planned to report serum concentrations of vitamin B12, homocysteine and methylmalonic acid and sources of clinical outcome of both routes of administration, oral and parenteral, giving mean differences and confidence intervals. For other outcome measures, relative risk with 95% confidence intervals or effect sizes will be reported.

We intended to assess sources of heterogeneity in order to determine whether variation observed in the results could be explained by chance alone. We intended to use the chi-squared test and the I-square test to examine evident heterogeneity between the trials (Higgins 2002). If significant heterogeneity was evident ($P < 0.1$), we could have attempted to determine reasons through subgroup and sensitivity analyses.

If in the future adequate data become available we will use this method of analysis.

Subgroup analysis and investigation of heterogeneity—We planned subgroups for the following:

- Newly diagnosed patients
- Patients already established on intramuscular treatment
- People over 65 years of age
- Patients who have had stomach or small bowel resection
- Vegetarians
- Patients taking anti-ulcer medication over long periods
- Patients with dementia
- Patients with acquired immunodeficiency syndrome

Sensitivity analysis—When relevant, we planned to repeat the analysis:

- excluding studies published in abstract form only;
- taking account of study quality, as specified abov;
- excluding any unusually long term or large studie;.
- excluding studies using the following filters: source of funding (industry versus other), country.

We planned to test the robustness of the results by repeating the analysis using different measures of effect size (risk difference, odds ratio etc.) and different statistical models (fixed and random effects models).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Data extraction—Two groups of researchers independently extracted data from the two randomised studies that met the inclusion criteria using piloted data extraction forms. The characteristics are described in the table Characteristics of included studies. We did not extract data from non-randomised studies or studies that clearly did not meet the inclusion criteria. The whole group checked all the relevant studies in relation to inclusion and exclusion criteria.

Language—Most of the publications were written in English (88%), but we found seven papers that we felt warranted closer scrutiny written in other languages: Italian (Aguzzi 1985; Migliorini 1979), French (Brassinne 1974; De La Fourniere 1997; Kaltenbach 2003), Danish (Bastrup-Madsen 1973) and Czech (Bezdickova 1997).

JVA and MF independently assessed the Italian studies. JVA and DP assessed the three French studies. BN and AMH independently assessed the Danish study. JVA and CCB assessed the English abstracts of the Czech study and this study was excluded on the basis of the abstract alone.

Results of the search—Our initial search included studies published before 2003. After the protocol was published, we decided to include the studies published during 2003 and 2004. After manually removing all duplicates, we pre-selected 797 abstracts identified by searches. We selected 41 abstracts for which the full paper was obtained and two studies met the inclusion criteria.

Handsearching: Searching the bibliographies of the selected articles and other relevant studies identified another 15 studies for which we obtained the full text.

A total of 56 studies were thus selected for review of the full paper.

Additional search strategies: Clinical experts (Dr Norberg, Dr Burr, Dr Dempsey and Dr Lederle) authors of relevant identified studies (Dr Andres, Dr Nyholm, Dr Bolaman and Dr Allen) and Vitamin B12 manufacturers (Goldshield Pharmaceuticals, Link Pharmaceuticals and Celltech Group) were contacted to enquire about other published or unpublished studies, ongoing trials and to obtain additional references. No additional studies were identified in this way.

Interrater agreement: Each stage of selection of studies was followed by discussions with the group. The process resulted in agreement in the pre-selection stage, the quality of the assessment, and in the data extraction phase. We did not use kappa statistic (Cohen 1960) because during the pre-selection process we obtained hard copies of any study independently identified by researchers. When assessing the methodological quality of the included studies kappa statistic was not calculated as just two studies met the inclusion criteria.

Included studies—Two randomised control trials (Bolaman 2003; Kuzminski 1998) fulfilled our inclusion criteria. Characteristics of these studies are shown in Characteristics of included studies

Study types: Two studies compared oral administration of vitamin B12 versus intramuscular administration of vitamin B12. The two studies were randomised controlled trials.

Participants: The trials recruited a total of 108 participants and followed up 93 of these from 90 days to four months. 52 participants were female (56%) and 41 were male (44%). Participants in both studies had low serum vitamin B12 levels and both were set in outpatient hospital clinics. The first study was carried out in USA by Kuzminski and colleagues (Kuzminski 1998) and the second in Turkey by Bolaman and colleagues (Bolaman 2003).

Kuzminski and colleagues recruited 38 patients with a mean age of 72 years for the oral group and 71 years for the intramuscular group. 28 of these patients had conditions that may

be associated with malabsorption from the gut (including seven with pernicious anaemia and three with ileal resection), although patients with inflammatory bowel disease and coeliac disease appear not to have been included.

Bolaman and colleagues recruited 70 patients with a mean age of 60 years for the oral group and 64 years for the intramuscular group. 35 of these patients had conditions affecting the ileum that may be associated with malabsorption from the gut. Again, however, patients with inflammatory bowel disease and coeliac disease appear not to have been included.

Patient inclusion and exclusion criteria in individual studies are outlined in Characteristics of included studies.

Interventions: The two studies compared oral administration of vitamin B12 versus intramuscular administration of vitamin B12. The duration of the intervention was the same as the duration of the follow up. The dose of oral vitamin B12 used by Kuzminski and colleagues was 2,000 mcg (Kuzminski 1998); Bolaman and colleagues used 1,000 mcg (Bolaman 2003). The dose of intramuscular vitamin B12 was 1,000 mcg in both studies and it was administered by nurses.

Outcome measures: Several primary outcomes measures were reported in the studies:

- Serum vitamin B12
- Haemoglobin
- Mean Corpuscular Volume (MCV)
- White Blood Cells (WBC)
- Platelet count
- Methylmalonic Acid
- Homocysteine
- Folate
- Serum creatinine
- Fasting serum gastrin
- Parietal and intrinsic factor antibodies
- Mini-Mental State Examination
- Neurologic assessment

Only one of the studies (Bolaman 2003) in addition reported about tolerability of medication (assessed by a haematologist and patient interviews), and costs, assessed by the authors using cost of the study drug and the injections.

Excluded studies—Fifty-four studies were excluded. Reasons for exclusion of studies are given in Excluded studies. The most common reason for exclusion was a non-randomised trial design (57%) or the study did not meet intervention criteria (35%).

Risk of bias in included studies

Further details of the methodological quality of the included studies can be found in Appendix 2.

Allocation—One of the studies (Kuzminski 1998) did not describe attempts to conceal the assignment of participants.

Patients were randomised using the block randomization method described by Altman (Altman 1999) to allocate participants (Bolaman 2003). The other study (Kuzminski 1998) stated that they used a statistical package for randomisation but did not provide further details.

Blinding—The two studies (Bolaman 2003; Kuzminski 1998) were not blinded, as patients knew whether they were taking oral or intramuscular medication since no placebo was used.

Incomplete outcome data—In the study by Kuzminski and colleagues (Kuzminski 1998), 38 participants were randomised but five participants were excluded from the final analysis because they were judged to have primary folate deficiency rather than Vitamin B12 deficiency. The final analysis included 18 participants in the oral group and 15 randomised to receive intramuscular treatment. Three participants randomised to receive intramuscular vitamin B12 had a total of seven samples excluded from the analysis because of an error in taking the specimen. However the samples were judged valid for assay of serum metabolites. The authors did not analyse according to intention to treat.

In the study by Bolaman and colleagues (Bolaman 2003), 70 participants were enrolled in the study but 10 were excluded because failure to appear to follow up. The final analysis included 26 participants in the oral group and 34 randomised to receive intramuscular treatment. The authors did not analyse according to intention to treat.

Other potential sources of bias

Sample size calculation: None of the studies reported a sample size calculation.

Length of follow-up: The length of follow up ranged from 90 days to four months. We consider this as insufficient because of the long biological half-life of body stores of vitamin B12. This is estimated to be more than 30 month (Basu 1996).

Effects of interventions

Two studies compared oral and intramuscular vitamin B12: Kuzminski and colleagues (Kuzminski 1998) reported neurologic and haematologic responses. Four of the eighteen participants randomised to receive oral vitamin B12 and four of the fifteen randomised to receive intramuscular vitamin B12 had a neurological response with a marked improvement or clearing of paresthesias, ataxia, or memory loss. Serum vitamin B12 levels were significantly higher in the oral (643 +/− 328 pg/mL) compared to the intramuscular group (306 +/− 118 pg/mL) at 2 months ($P<0.001$). The difference was even greater at four months (1,005 +/− 595 vs. 325 +/− 165 pg/mL; $P< 0.0005$). Serum methylmalonic acid

concentrations decreased to < 3 SD above the normal range in all participants except one in the oral and two in the intramuscular group. Mean concentrations of the metabolites were not significantly different between the oral and the intramuscular groups, except at four months, when the value was higher in the intramuscular group (P< 0.05). Elevated serum total homocysteine decreased to 3 SD above the normal range in most participants, but the decrease was over four months in the oral group and during the first month in the intramuscular group. However, in two patients in each group the response was not optimal.

Bolaman and colleagues (Bolaman 2003) reported neurologic and haematologic responses. Both groups receiving oral or intramuscular vitamin B12 reported improvements of cognitive function, sensory neuropathy and vibration sense but the difference between both groups was not statistically significant. Serum vitamin B12 levels increased in those receiving oral and those receiving intramuscular vitamin B12 for 90 days. The authors reported a statistically significant difference between day 0 and day 90 within both groups (P< 0.001) but did not analyse differences between both groups.

Heterogeneity and subgroup analyses—It was not possible to investigate heterogeneity or to do subgroup analysis as the four studies differed markedly in terms of interventions. Sensitivity analyses were not possible due to the small number of studies that met the inclusion criteria. We could have included more studies if we had considered participants with normal vitamin B12 levels at study entry but the objective of the review was to look at the use of vitamin B12 for the treatment of vitamin B12 deficiency. Adverse effects, acceptability and quality of lifeOnly one of the studies mentioned adverse effects and tolerability (Bolaman 2003). In this study, the authors stated that the oral treatment was better tolerated but they did not report on how they assessed tolerability. None of the studies gave an account of the effect of the intervention in the quality of life of participants. Costs were reported in one of the included trials (Bolaman 2003). In the trial, the cost of the treatment was $ 80 (66 Euro) per participant in the oral group and $ 220 (184 Euro) per participant in the intramuscular group (P< 0.001). Authors did not report which economic analysis was performed.

DISCUSSION

Summary of main results

We identified two randomised controlled trials directly relevant to the study question. The follow up period ranged between 90 days to four months. A total of 108 patients with vitamin B12 deficiency participated in these studies. After consideration of study populations, treatments, outcome measures and follow up, we concluded that meta-analysis was not appropriate. A major consideration was heterogeneity of oral treatment regimes and diverse eligibility for study entry.

The authors of the two studies comparing oral with intramuscular administration of vitamin B12 concluded that oral vitamin B12 was as effective as the intramuscular treatment. Kuzminski and colleagues (Kuzminski 1998) concluded that 2000 mcg daily of oral cyanocobalamin was as effective or even superior to 1000 mcg of the same medication administered intramuscularly every month. Bolaman and colleagues (Bolaman 2003)

concluded that 1000 mcg of oral or intramuscular vitamin B12 daily for 10 days followed by once weekly for four weeks and once monthly for life was equally effective to treat patients with megaloblastic anaemia. Neither study was blinded. However, the conclusions were based on haematological as well as neurological responses to both treatments and laboratory assessments were likely to have been blinded. A crucial aspect our study addresses is whether or not patients with conditions that might cause malabsorption may be safely treated with oral vitamin B12 in primary care. This was difficult to ascertain because in the trials numbers are small, follow up short and trials did not include patients with common conditions that might interfere with absorption in the terminal ileum such as Crohn's disease, coeliac disease or ulcerative colitis. Three patients with ileal resection and seven with pernicious anaemia were included in one of the studies. Despite these cautions, we did find evidence of a satisfactory short term response to oral vitamin B12 replacement even in patients with some conditions, mainly affecting the upper gastrointestinal tract that may be associated with malabsorption.

Overall completeness and applicability of evidence

The studies included older participants with a mean age ranging from 60 to 72. This is consistent with the higher prevalence of Vitamin B12 deficiency amongst the elderly (Rajan 2002; van Walraven 1999). However, the regimen described in the two studies, will be particularly challenging for the elderly with dementia. None of the studies was conducted in Primary Care where most of the patients with vitamin B12 deficiencies are treated; this makes the generalisability of the results more difficult. Another factor affecting generalisability is that the four studies used different treatment regimes and used strict and numerous exclusion criteria.

The study conducted by Kuzminski and colleagues (Kuzminski 1998) used injectable cyanocobalamin and not hydroxocobalamin. The bioavailability of the water solution of cyanocobalamin used is much lower than that of more usual injectable preparations such as hydroxocobalamin. For example, Glass and co-workers showed that 69% of a dose of 1000 mcg of cyanocobalamin given as injection was recovered in the urine over 72 hours. The corresponding percentage after an injection of 1000 mcg of hydroxocobalamin was 27% (Glass 1961). The amount of retained B12 would therefore be quite low in the injection group in this particular study. This probably explains why oral B12 appeared to be more effective than this particular injectable preparation.

In one of the studies using higher doses of oral vitamin B12 (Bolaman 2003), the authors reported that no adverse events occurred. This is consistent with previous studies (Hathcock 1991). The outcomes were limited and the length of follow up was probably too short to demonstrate effectiveness of the oral treatment, this makes the applicability of the results difficult.

Potential biases in the review process

This body of evidence has serious limitations as it includes only two open studies with relatively short follow up periods (90 days and four months) and small number of participants (n = 38 and n = 70) with some attrition. In addition, there are methodological

limitations to both studies identified by our search strategy. In one of the studies (Kuzminski 1998) the method of randomisation it is not described. Allocation concealment was adequate in just one study (Bolaman 2003). Intention to treat analysis and blinding was not performed or mentioned in any of the studies. We did not carry out meta-analysis because of heterogeneity of designs, dosages and participants.

Agreements and disagreements with other studies or reviews

We identified many studies assessing the effectiveness of oral vitamin B12, but they were not randomised. The studies, dating from the early 50's to recently, were mainly before and after studies and all show that patients with vitamin B12 deficiency respond to oral vitamin B12 replacement therapy in clinical and/or laboratory terms (Andres 2001; Andres 2003a; Berlin 1968; Brody 1959; Chalmers 1958; Conley 1952; Conley 1955; Hemsted 1958; Kondo 1998 ; McIntyre 1960; Reisner 1955; Spies 1949; Unglaud 1955; Ungley 1950; Verhaeverbeke 1997; Waife 1963). However, it is not clear in most of these studies how many included patients suffered from conditions that may cause malabsorption.

AUTHORS' CONCLUSIONS

Implications for practice

The limited evidence identified in this systematic review shows that ***high doses*** of oral vitamin B12 (2000 mcg) daily are as effective as the intramuscular administration (Kuzminski 1998) in obtaining haematological and neurological responses in patients with vitamin B12 deficiency. High doses of oral vitamin B12 (1000 mcg) initially daily and thereafter weekly and then monthly are also as effective as intramuscular vitamin B12 (Bolaman 2003). The included studies also showed limited evidence for a satisfactory haematological, biochemical and clinical short term response for oral B12 replacement in some patients with conditions associated with malabsorption.

Current clinical practice in UK and in most countries is to prescribe vitamin B12 in the intramuscular form for the treatment of vitamin B12 deficiency. This has been the norm for the last 50 years despite several non-randomised studies in the early 1950's demonstrating satisfactory responses to oral treatment and the fact that there is considerable experience in Sweden in using oral vitamin B12. In 1998, the study by Kuzminski et al. (Kuzminski 1998) was the first randomised controlled trial to show that in achieving a satisfactory neurological, haematological and biochemical response, daily high doses of oral vitamin B12 were as effective or even more effective than intramuscular vitamin B12 when treating patients with vitamin B12 deficiency.

Generalised oral vitamin B12 treatment might benefit many patients in terms of fewer visits to health carers and reduced discomfort associated with injections. Nursing time would be released for treating other patients. However, adherence and monitoring will remain important considerations, regardless of route of administration.

Implications for research

The above evidence has not been sufficient to change practice in most countries. A further large, pragmatic trial in a primary care setting is needed to determine whether oral vitamin B12 is effective in patients with major common cases of malabsorption and to provide additional evidence regarding cost effectiveness.

In addition, clinicians are often concerned about patient preferences regarding treatment route. General Practitioners commonly report that patients receiving intramuscular vitamin B12 are reluctant to reduce the frequency of their injections or change from intramuscular to oral vitamin B12 replacement, despite having serum vitamin B12 levels several times the normal range. Many patients receive vitamin B12 injections more often than the recommended three month interval (Cochrane 1971; Fraser 1995; van Walraven 1999). Some individuals started on vitamin B12 for 'tiredness', but with normal haematological and biochemical parameters, report feeling better on the injections and are reluctant to stop them. This suggests that intramuscular B12 may carry additional psychotropic effects for patients, exceeding those associated with normalisation of serum vitamin B12 serum levels. In a recent qualitative and quantitative study, 73% of patients were willing to try oral vitamin B12 and of those who tried the oral therapy 71% wished to permanently switch. They mentioned travel inconveniences as reasons for preferring the oral route (Kwong 2005). However, in another non-randomised control trial, researchers attempted to convert patients in primary care from intramuscular to oral vitamin B12 replacement but only half agreed to participate in the study (Nyholm 2003). Possible psychotropic effects are important because they may make General Practitioners and patients reluctant to change to oral therapy, despite evidence that this route is as effective and probably cheaper than the intramuscular route. A deep understanding of patient's preferences, explaining possible psychotropic effects of intramuscular vitamin B12 therapy, and developing effective ways of reaching shared decisions with patients is probably the way forward.

Further research is therefore needed to avoid perpetuating oral vitamin B12 replacement as one of "medicine's best kept secrets" (Lederle 1991).

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* Indicates the major publication for the study

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bolaman 2003	
Methods	Allocation: randomised Observation period: 90 days
Participants	Patients with megaloblastic anaemia due to cobalamin deficiency Numbers: 70 patients enrolled, 10 excluded. Outcomes measured for 60 patients. 26 oral group. 34 intramuscular group. 14 patients with atrophic gastritis, 7 with chronic antral gastritis, 7 with chronic pangastritis, 6 with alkaline reflux gastritis and 1 with erosive gastritis Age: Mean age 60 (+/−15) for the oral group and 64 (+/−10) for the intramuscular group Inclusion criteria: • Serum cobalamin level <160pg/mL • Megaloblastic anaemia. • MCV>94 fL Exclusion criteria:

	• Vomiting and/or diarrhoea • Alcohol use >40 g/d • Incapacity to give informed consent • History of malignancy • Folate deficiency • Inability to ingest oral medication • Use of medication might interfere with folate metabolism • Pregnant or possibly pregnant • Breastfeeding
Interventions	1000 mcg cobalamin oral or intramuscular once daily for 10 days. After 10 days, once a week for 4 weeks and after that patients were asked to continue treatment once a month indefinitely
Outcomes	Primary Outcomes: • Serum cobalamin • Mini-Mental State Examination • Neurologic assessment Additional Outcomes: • Haemoglobin • MCV • WBC • Platelet count • Tolerability • Costs • Side effects not reported
Notes	Not blinded

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Kuzminski 1998	
Methods	Allocation: randomised Observation period: 4 months
Participants	Newly diagnosed cobalamin deficient patients Numbers: 38 randomised. Outcomes measured for 33 patients 17 patients with chronic atrophic gastritis, 7 with pernicious anaemia, 3 with ileal resection, 1 with gastric stapling Age: Mean age 72 (+/− 11) for the oral group and 71 (+/− 15) for the intramuscular group Inclusion criteria: • Serum cobalamin level <160pg/mL • Elevation of serum methylmalonic acid, total homocysteine or both metabolites >3 SD's above the mean in normal controls Exclusion criteria: • Location outside immediate geographical area • Incapacity to give informed consent • Refusal to participate

	• Associated life-threatening illness • Primary Folate deficiency	
Interventions	1000 mcg intramuscular cyanocobalamin on days 1, 3, 7, 10, 14, 21, 30, 60 and 90 2000 mcg oral cyanocobalamin daily for 120 days	
Outcomes	Primary Outcomes: • Serum cobalamin • Neurologic responses Additional Outcomes: • Methylmalonic Acid • Homocysteine • Side effects not reported	
Notes	Not blinded	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

MCV. Mean Corpuscular Volume

WBC. White Blood Cells

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adachi 2000	Non-randomised study
Aguzzi 1985	Randomised, placebo-controlled double-blinded study assessing the effectiveness of a product mixture containing cyanocobalamin in the treatment of age-dependent psychic regression. No evidence that patients were vitamin B12 deficient
Altay 1999	Non-randomised study
Andres 2001	Non-randomised study
Andres 2003	
Andres 2003a	Non-randomised study
Andres 2003b	Same patients as in Andres 2003, letter in a different publication
Andres(2) 2003	
Anonymous 1997	Review of treatments of diabetes. Non-randomised study
Bastrup-Madsen 1973	Randomised study but comparing intramuscular hydroxocobalamin and intramuscular cyanocobalamin
Berlin 1968	Non-randomised study
Bezdickova 1997	Non-randomised study
Boddy 1968	Cross-over study comparing subjects without vitamin B12 deficiency
Brassinne 1974	Non-randomised study
Brody 1959	Non-randomised study
Brody 1967	Non-randomised study
Chalmers 1958	Non-randomised study
Chalmers 1965	Study comparing intramuscular injections of hydroxocobalamin and cyanocobalamin
Conley 1952	Non-randomised study

Study	Reason for exclusion
Conley 1955	Non-randomised study
De La Fourniere 1997	Randomised, placebo-controlled double-blinded study assessing use of intramuscular vitamin B12 in dementia
Ellis 1973	Randomised, cross-over double-blinded study comparing intramuscular hydroxocobalamin and intramuscular placebo in tiredness
Glass 1966	Non-randomised study
Hedstrand 1969	Non-randomised study
Hemsted 1958	Study comparing intramuscular injections monthly with oral treatment daily. The study does not state whether patients were randomised
Hughes 1970	Randomised, placebo-controlled double blinded study comparing intramuscular hydroxocobalamin with placebo
Hvas 2003	Randomised, placebo-controlled double-blinded study comparing intramuscular vitamin B12 with placebo
Kaltenbach 2003	Non-randomised study
Killander 1968	Non-randomised study
Kondo 1998	Non-randomised study
Kwok 1998	Randomised controlled study comparing intramuscular cyanocobalamin with no treatment
Mader 1988	Randomised, placebo-controlled double-blinded study using an oral multivitamin preparation containing folic acid in headaches. No data available regarding vitamin B12 levels
Mann 1987	Randomised, placebo-controlled blinded study using a multivitamin/mineral preparation containing folic acid. Most of the patients were had not vitamin B12 deficiency
Martin 1992	Non-randomised study
Mauro 2000	Randomised, placebo-controlled double-blinded study studying efficacy of intramuscular vitamin B12 in the treatment of low back pain
McIntyre 1960	Non-randomised study
Migliorini 1979	Randomised controlled double-blinded study looking at the effect of intramuscular vitamin B12 in pain
Naurath 1995	Double-blinded placebo controlled study using an intramuscular multivitamin preparation
Nyholm 2003	Non-randomised study
Pathy 1972	Non-randomised study
Reisner 1955	Non-randomised study
Rhode 1995	Study comparing different doses of oral vitamin B12 treatment. No placebo group. No randomisation apparent
Ross 1954	Non-randomised study
Saltzman 1993	Unable to locate study as part of a supplement
Seal 2002	Randomised controlled study comparing different doses of oral cyanocobalamin with oral placebo
Skouby 1970	Non-randomised study
Slot 1997	Non-randomised study
Spies 1949	Non-randomised study
Tin 1978	Randomised, placebo-controlled double-blinded study comparing the effect of intramuscular cyanocobalamin and placebo on physical performance
Tudhope 1967	Randomised study comparing intramuscular hydroxocobalamin and intramuscular cyanocobalamin

Study	Reason for exclusion
Ubbink 1994	Randomised, placebo-controlled blinded study looking at the effect of vitamin supplementation on hyper-homocysteinemia. Some patients receiving vitamin B12 were not vitamin B12 deficient
Unglaud 1955	Non-randomised study
Ungley 1950	Non-randomised study
van Asselt 2001	Non-randomised study
Verhaeverbeke 1997	Non-randomised study
Waife 1963	Non-randomised study

DATA AND ANALYSES

This review has no analyses.

Appendix 1

Search strategy

Electronic searches	
Unless otherwise stated, search terms were free text terms; exp = exploded MeSH: Medical subject heading (Medline medical index term); the dollar sign ($) stands for any character(s); the question mark (?) = to substitute for one or no characters; tw = text word; pt = publication type; sh = MeSH: Medical subject heading (Medline medical index term); adj = adjacency.	
1	vitamin$ b12.tw.
2	vitamin$ b 12.tw.
3	cobalamin$.tw.
4	hydroxycobalamin$.tw.
5	cyanocobalamin$.tw.
6	betolvex.tw.
7	exp Vitamin B 12/ae, cl, ct, tu [Adverse Effects, Classification, Contraindications, Therapeutic Use]
8	exp Hydroxocobalamin/ae, tu [Adverse Effects, Therapeutic Use]
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp Vitamin B 12 Deficiency/
11	vitamin B12 deficienc$.tw.
12	vitamin B 12 deficienc$.tw.
13	B 12 deficienc$.tw.
14	b12 deficienc$.tw.
15	10 or 11 or 12 or 13 or 14
16	randomized-controlled trial.pt.
17	controlled-clinical trial.pt.
18	randomized-controlled-trials.sh.
19	random allocation.sh.
20	double-blind method.sh.
21	single-blind method.sh.
22	or/16–21
23	animal.sh.
24	human.sh.
25	23 not 24
26	22 not 25
27	clinical trial.pt.
28	exp clinical trials/
29	(clinic$ adj25 trial$).tw.
30	((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
31	Placebos.sh.
32	placebo$.tw.
33	random$.tw.
34	research design.sh.
35	(latin adj square).tw.
36	or /27–35
37	36 not 25

Electronic searches	
38	37 not 26
39	exp evaluation studies/
40	follow-up studies.sh.
41	prospective studies.sh.
42	(control$ or prospectiv$ or volunteer$).tw.
43	cross-over studies.sh.
44	comparative study.sh.
45	or/39–44
46	45 not 25
47	46 not (26 or 38)
48	26 or 38 or 47
49	9 and 15 and 48
50	from 49 keep 1–627

Appendix 2

Methodological quality of included studies

Study	Randomisation	Alloc. Conceal.	Blinding	N. Randomised	Withdrawals	Intent_to_treat	Follow-up
Kuzminski 1998	Unclear	Unclear	No	38	5	No	4 months
Bolaman 2003	Block randomisation method	Probably adequate	No	70	10	No	90 days

Appendix 3

Data extraction sheet

Items
Screener's name
Study number and name
Author
Publication
Language of Publication
Year of publication
Country
Type of study (case control, case series, article, RCT …)
Treatments
Inclusion - Exclusion criteria
Numbers recruited
Numbers randomised
Numbers loss to follow up
Why? (reasons)
Numbers excluded
Why? (reasons)
Withdraws
Why? (reasons)
Outcomes measures (bioquemical, functional)
Randomisation. If yes:
* Length of follow up
* Follow up points
* Side effects
* N. Evaluated in each group
* N. Responded in each group
Quality (Cochrane criteria)
a) low risk of bias (plausible bias is unlikely to alter the results seriously)
b) moderate risk of bias (plausible bias raises some doubt about the results)
c) high risk of bias (plausible bias seriously weakens confidence in the results)
Blinding. If yes:
* Method of blinding
Intention-to-treat analysis
Additional treatment (co-interventions)
Power calculation (stats)