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SHORT COMMUNICATION

Comparing the Effectiveness of Oral Supplementation and Intramuscular Injection of Vitamin B_{12} for Treating Cobalamin Deficiency: Systematic Review and Meta-analysis

Kyung Eun Lee[1§], Hyo Jin Park[2], Yinghua Cui[3]

[1] *Yeungnam University College, School of Nursing, Daegu, South Korea*
[2] *Yeungjin College of Nursing, Daegu, South Korea*
[3] *Yanbian University of Science & Technology School of Nursing, Yanji, China*

ABSTRACT

Introduction: The common treatments for vitamin B_{12} (Vit.B_{12}) deficiency are oral supplementation (OS) and intramuscular (IM) injection. However, there have been debates on which treatment is more effective. Therefore, this analysis is aimed at comparing the effectiveness of OS and IM injection using systematic review and meta-analysis. **Methods:** A search was undertaken in the Cochrane Library, MEDLINE, EMBASE, and KoreaMed for randomised controlled trials (RCTs) on the study subject. We included papers that compared OS and IM injection methods for vitamin B_{12} treatment for cobalamin deficient patients. Changes in vitamin B_{12} serum levels before and after the treatments were compared. SPSS program version 18.0 and Review Manager 5.2 were used. **Results:** The search revealed only three appropriate studies for our analysis, involving a total of 141 patients, out of whom, 66 were given OS and 75 IM injection. The standardised mean difference (SMD) between OS and IM injection was 0.14 (95% CI = -0.20, 0.48, p = 0.42). In considering tolerability, adverse events, and cost, OS was found to be better than IM injection. **Conclusions:** OS is recommended over IM injection for Vit.B_{12} treatment method.

Key words: Cobalamin, meta-analysis, systematic review, vitamin B_{12} vitamin B_{12} deficiency

INTRODUCTION

Vitamin B_{12} (vit.B_{12}), also called cobalamin, is a water-soluble vitamin and plays a key role in the formation of red blood cells and neurological function. If Vit. B_{12} deficiency is not treated properly, it may cause anaemia, fatigue, weakness, constipation, appetite loss, weight loss, mood disturbance, neuropsychiatric problems, and neurological complications (Butler, *et al*., 2006; National Institutes of Health, 2016).

The most common treatments for cobalamin deficiency are oral supplementation (OS) and intramuscular (IM) injection. There are some adverse effects of OS, such as constipation and heartburn, but has to be taken on a daily basis. Additionally, there is no way to predict vit.B_{12} uptake at the terminal ileum. Therefore, IM injection has traditionally been used more often (Butler *et al*., 2006; Castelli *et al*., 2011). However, IM injection can also cause pain (during the injection) or

* Correspondence: Kyung Eun Lee; Email: *lkeone@hanmail.net*

bleeding. In addition, it can be dangerous to patients receiving anti-coagulant treatment. Most importantly, patients must visit a hospital to get injections on a monthly basis (Butler *et al*., 2006; Castelli *et al.,* 2011; Masucci & Goeree, 2013).

Butler *et al.* (2006) published a 'systematic review' of OS and IM injection, stating which method is more effective. However, the authors did not conclude which method was more effective. To this day, there are no guidelines on choosing a method for vit.B_{12} treatments. Debates have been ongoing on their efficacy, but the use of OS has increased compared to IM injection. Therefore, it is necessary to compare the effectiveness of OS and IM injection with a systematic review and meta-analysis.

METHODS

Systematic search

Searches were undertaken in The Cochrane Library, MEDLINE, EMBASE, KoreaMed. The search strategy used the following terms: exp vitamin B12/ OR vitamin*B12.mp. OR vitamin*B12.mp. OR cobalamin*.mp. OR mecobalamin*.mp. OR methylcobalamin*. mp. OR exp Hydroxocobalamin/ OR hydroxocobala-min*.mp. OR eritron*.mp. OR betolvex.mp. AND exp vitamin B12 Deficiency/ OR vitamin* B12 deficiency. mp. OR vitamin* B12 deficiency.mp. OR vitamin* B12 deficient.mp. OR vitamin* B12 deficiency.mp.

The search was limited to research using randomised control trials (RCTs). Language restriction was not used at the first stage. We attempted to identify additional studies not found by the primary search method by reviewing the reference lists from the identified studies. Unpublished studies were not included in the search.

Selection of studies

The study's inclusion and exclusion criteria were determined before the systematic search. Two authors, independently, evaluated the abstracts and results of articles obtained from the initial search. At this stage, articles that were clearly not relevant to our criteria were excluded. Disagreements on inclusion of the articles were resolved by discussion between the two authors. If an agreement could not be reached, the dispute was resolved with a help of another investigator who was ignorant of the first and the second authors' results.

We included papers that had used RCTs to compare OS and IM injection methods as vit.B_{12} treatments for cobalamin deficient patients. We excluded (1) literature containing patients using vit. B_{12} supplementation to prevent different diseases; (2) studies that included any intervention except for OS and IM injection; (3) articles containing animal experiments; (4) papers written in any language except for English or Korean; and (5) review articles, letters, comments, or case reports that lacked raw data.

Quality assessment

The quality assessment of the selected literature was based on 'Assessing Risk of Bias' from the Cochrane collaboration (Higgins *et al*., 2011).

Data synthesis and analysis

In order to perform the meta-analysis we compared the changes in the vit. B_{12} level of the patients before and after the treatments. Because of the different measurement standards, for the integrated estimation, mean ± standard deviation (SD) and standardised mean difference (SMD) of cobalmin serum levels were used. We used SPSS program version 18.0 and Review Manager 5.2. The weighted mean differences with 95% confidence interval (CI) were determined and reported for continuous data.

Heterogeneity was determined by using the chi-square test and the I^2 test. I^2 values range between 0 and 100%, with 0 representing perfect homogeneity among included studies and 100% representing the highest degree of heterogeneity. A $p < 0.10$ for the chi-square test was interpreted as evidence of heterogeneity.

RESULTS

Description of studies that met inclusion criteria

The process of identifying relevant studies is summarised in Figure 1. Finally, three studies met our inclusion criteria. The total number of recruited patients was 158 in the three studies with 141 patients completing the study protocol. Sixty-six patients were given OS, while 75 patients were given IM injection. Each study had different standard serum vit.B_{12} levels. Two studies used the same intervention strategy where a one-time dosage of 1,000 μg for the same period, 90 days, was administered to both the groups. The serum vit.B_{12} level in both

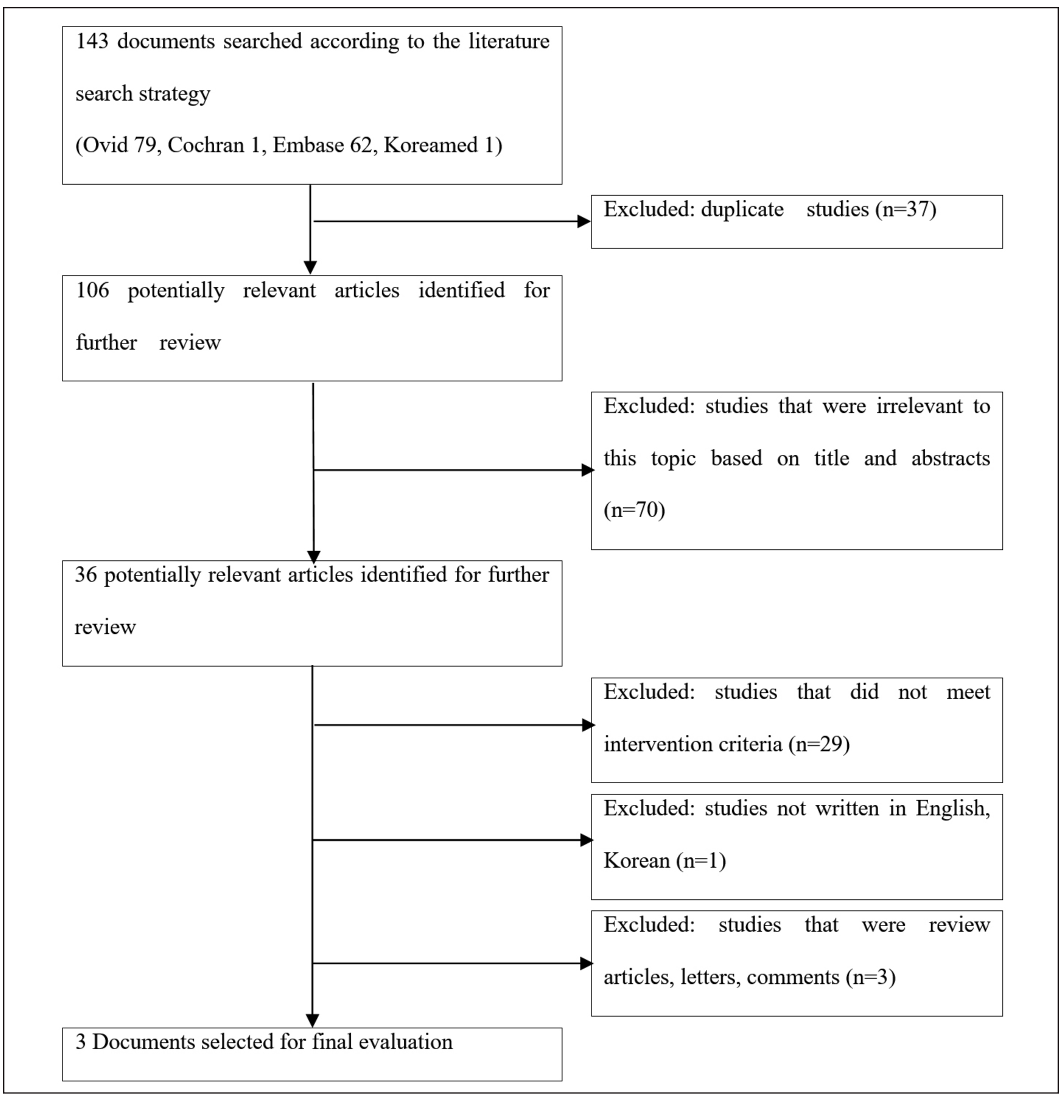

Figure 1. Flowchart of the article selection process

groups was evaluated 120 days after the first administration. The third study used a different method with a one-time dosage of 2,000 µg for 120 days for the OS group whereas only 1,000 µg was used in the IM injection group for 90 days (Table 1).

Risk of bias in included studies

None of these studies mentioned allocation concealment, blinding of participants and personnel, or blinding of the outcome assessment. One study did not have any missing values. The other two studies had missing values, only one study explained its missing values. The additional risk of bias was not mentioned in any of these studies

Effects of cobalamin on serum levels

Subsequent to the two administration methods, IM injection resulted in a bigger increase in serum Vit.B_{12} levels compared to OS in two of the studies, whereas the third study showed more effective results for OS. However, all three studies showed that the serum vit.B_{12} level increased to the normal range regardless of the amount of dosage and the period of administration in both groups (Table 2). The SMD was 0.14 (95% CI = -0.20, 0.48, p = 0.42) for OS and IM injection, which indicates the absence of any statistically significant difference between the two methods. However, there is high heterogeneity in the literature (I^2 = 85%). Only one article mentioned that the OS is more effective than the IM injection (Figure 2).

Effects of neurologic responses

The improvements in neurologic responses after cobalamin administration were reported in two of the articles. In the study of Kuzminski *et al.* (1998), both treatments showed improvements in the neurologic responses after the interventions but the statistical significance was not explained. The study by Bolaman *et al.* (2003) also indicated an improvement in neurologic responses after the treatments in both groups but did not explain the statistical significance of the improvement.

Analysis of tolerability/adverse of events

Tolerability and adverse events after vit. B12 interventions were assessed in two of the articles. There were no adverse events resulting from OS or IM injection in the study of Bolaman *et al.* (2003). On the other hand, the study by Castelli *et al.* (2011) reported adverse effects such as mild to moderate intensity abdominal pain, constipation, and diarrhoea. More than half of the patients in both groups experienced adverse effects: 54.2% in the OS group and 57.7% in the IM injection group.

Costs

The cost of cobalamin treatments with OS and IM injection were compared in one study. Bolaman *et al.* (2003) reported that OS is more expensive than IM injection treatment (p < 0.001).

DISCUSSION

Vit.B_{12} deficiency has been commonly treated with IM injection method but of late, the OS method has been increasingly used resulting in much debate on which treatment is better. Based on our analysis of previous studies, we found IM injection intervention method had better results in two studies, while the OS intervention had more effective results in the third study However, because of large heterogeneity (X^2 = 13.52, p < 0.001, I^2 = 85%), we were able to compare only two studies, that of Bolaman *et al.* (2003) and Castelli *et al.* (2011), as these two studies used the same amount of dosage with a similar period of cobalamin administration in both treatment groups. There was no heterogeneity (X^2 = 0.05, p = 0.83, I^2 = 0%) and the effect size of the OS group was -0.17 (95% CI = -0.05, 0.21) compared to the IM injection group. However, there was no statistically significant difference (p = 0.38). Bolaman *et al.* (2003) was given a weighting of 55.2%

Table 1. Summary of characteristics of the studies

Author (year)	*Location*	*Design*	*Subjects*	*Number of subjects*	*Follow-up*	*Outcomes*
Kuzminski *et al.*(1998)	USA	RCT	Serum cobalamin < 160 pg/mL	38 (Oral: 18, IM: 15, Withdrawal: 5)	120 days	Serum level of vitamin B_{12}, hematocrit, MCV, folate, methylmalonic acid, and total homocysteine
Bolaman *et al.* (2003)	Turkey	RCT	Anemia due to cobalamin deficiency Serum cobalamin < 160 pg/mL	70 (Oral: 26, IM: 34, Withdrawal: 10)	90 days	Serum level of vitamin B_{12}, Hb, MCV, WBC count, and platelet count
Castelli *et al.* (2011)	USA	RCT	Serum cobalamin < 350 pg/mL	50 (Oral: 22, IM: 26, Withdrawal: 2)	91 days	Serum level of vitamin B_{12}, homocysteine, methylmalonic acid

Notes: Oral; oral supplementation, IM; intramuscular injection

Table 2. Baseline and changes in vitamin B_{12} serum level according to the administration methods

Author (year)	*Oral*				*IM*			
	n	Dose	Baseline (M±SD, pg/mL)	Changes (M±SD, pg/mL)	n	Dose	Baseline (M±SD, pg/mL)	Changes (M±SD, pg/mL)
Kuzminski *et al*. (1998)	18	2,000 μg 1/day for 120 days	93±46.0	904.4±585.8	14	1,000 μg on days: 1,3,7,10,14,21,30,60,90	95.0±92.0	230.0±188.9
Bolaman *et al*. (2003)	26	1,000 μg 1/day for 10 days, after 10 days, 1/week for 4 weeks, and then 1/month	72.9±54.8	140.9±62.7	34	1,000 μg 1/day for 10 days, after 10 days, 1/week for 4 weeks, and then 1/month	70.2±59.1	155.3±71.7
Castelli *et al*. (2011)	22	1,000 μg 1/day for 90 days	285.5±54.2	1,673.5±935.4	26	1,000 μg on days: 1,3,7,10,14,21,30,60,90	262.0±54.61	1,791.5±950.5

Oral; oral supplementation, IM; intramuscular injection

	Oral			IM injection				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
(10) Bolaman, 2003	140.9	62.7	26	155.3	71.7	34	44.6%	-0.21 [-0.72, 0.30]
(14) Castlli, 2011	1,673.5	935.4	22	1,791.5	950.5	26	36.2%	-0.12 [-0.69, 0.45]
(53) Kuzminski, 1998	904.4	585.8	18	230	188.9	15	19.2%	1.46 [0.67, 2.24]
Total (95% CI)			**66**			**75**	**100.0%**	**0.14 [-0.20, 0.48]**

Heterogeneity: Chi² = 13.52, df = 2 (P = 0.001); I² = 85%
Test for overall effect: Z = 0.81 (P = 0.42)

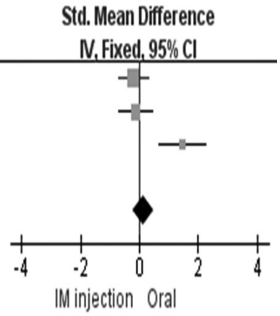

Figure 2. Combined result of meta-analysis for the mean difference (95% CI)

while Castelli *et al.* (2011) was given a weighting of 44.8%.

On the other hand, in the study by Kuzminski *et al.* (1998), a comparison of the effectiveness between two groups was constrained by the different dosage. A dose of 2,000 µg was administered to patients who received OS daily for 120 days and 1,000 µg was administered to patients who received IM injection per time for 90 days. Nevertheless, they showed that IM injection was a better method than OS. All of the three studies showed improvements in the serum cobalamin level up to a normal range subsequent to the intervention of either method, dosage, or period. Therefore, both treatments were considered as effective intervention methods to elevate and maintain normal serum cobalmin levels.

In the studies by Kuzminski *et al.* (1998) and Bolaman *et al*. (2003), OS and IM injection methods improved the patients' neurologic responses. In relation to tolerability and adverse effects, some patients experienced mild or moderate adverse events in the study of Castelli *et al.* (2011). In their study, 54.2% of the OS and 57.7% of the IM injection group showed adverse effects, and three subjects in the IM injection group showed severe adverse effects. From the perspective of cost, the study of Bolaman *et al*. (2003) reported that OS was more economical than IM injection method ($p < 0.001$). This result was similar to the results obtained by a recent study of Masucci & Goeree (2013).

A limitation of our study was that we only carried out the search through typical databases such as the Cochrane Library, MEDLINE, EMBASE, and KoreaMed. Finally, only three studies which met all our inclusion criteria were selected, but only the results from two studies were compared while the third study was excluded for its heterogeneity. Despite the small number of studies involved, this study is significant because only RCTs were selected and the B_{12} deficient patients had no other interventions except for OS and IM injection administration of vit.B_{12}.

CONCLUSION

Vitamin B_{12} serum level was improved to the normal range after OS and IM injection for vit.B_{12} deficient patients but no significant differences were found. Neurologic responses also improved under both treatments. However, taking into consideration tolerability, adverse events, and costs, OS showed comparatively better results. Therefore, OS is recommended for vitamin B_{12} treatment of cobalamin deficient patients.

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Conflict of interest

There is no conflict of interest to be declared.

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