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Comparative effectiveness of vitamin D supplementation via buccal spray versus oral supplements on 25(OH)D concentrations: a systematic review

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Abstract
Vitamin D (vitD) deficiency is the most common nutritional deficiency worldwide. Most patients are treated with oral vitD capsules (either vitD2 or vitD3). A few studies have reported equal efficacy of buccal spray vitD. This is a new formulation that is absorbed via the oral mucosa into the systemic circulation, bypassing the gastrointestinal route. The main objective of this systematic review was to identify RCT evidence for the comparative effectiveness of buccal spray versus oral vitD on serum 25-hydroxyvitaminD [25-OHD] concentrations and any adverse effects of buccal spray vitD. We have published an a priori protocol using Joanna Briggs Institute (JBI) methodology (PROSPERO CRD42018118580). A three-step search strategy to identify RCTs was conducted, which reported serum 25-OHD concentrations from five databases from 2008–2018. Retrieved abstracts were screened; included papers imported into JBI SUMARI and assessed for study quality (GRADE) by two authors. Meta-analysis was planned. Three RCTs met our inclusion criteria. Due to heterogeneity of studies, meta-analysis was not possible. In a RCT crossover study, mean serum 25-OHD concentrations were significantly higher in patients with malabsorption syndrome (n = 20) on 1000IU buccal spray + 117.8%(10.46, 95% CI6.89,14.03ng/ml) vs.1000IU oral vitD3 + 36.02%(3.96, 95%CI2.37, 5.56ng/ml) at 30days ($p < 0.0001$). Mean serum 25-OHD were also significantly higher in healthy adults (n = 20) on buccal spray + 42.99%(7.995, 95%CI6.86,9.13ng/ml)vs.oral vitD3 + 21.72%(4.06, 95%CI3.41,4.71ng/ml) at 30days ($p < 0.0001$). In another RCT crossover study, ANCOVA revealed no significant difference in the mean and SD change from baseline total 25-OHD concentrations in adults (n = 22) on 3000IU buccal spray vs. 3000IU oral vitD3 + 44%,26.15 (SD17.85) vs. + 51%,30.38 (SD17.91)nmol/l, respectively;$F = 1.044$, adjusted $r^2$0.493,$p = 0.313$ at 4 weeks. In a RCT, 800IU buccal spray was equally effective as 750IU oral vitD3 in children with neurodisabilities(n = 24) at 3 months. Both groups had a significant increase in 25-OHD; 11.5 ng/ml(median8–19) to 26.5(13.6–39)ng/ml and 15.5ng/ml(8–20) to 34.5(22–49) ng/ml, respectively ($z = 150$;$p < 0.0001$). The overall certainty of evidence was very low to moderate. No adverse effects were reported. The evidence from these studies suggests that 800IU-3000IU doses of buccal spray vitD3 given daily may be an effective alternative as oral vitD3 in obtaining short-term haematological responses in serum 25-OHD concentrations. Buccal spray vitD3 may be a useful alternative for patients with intestinal malabsorption or dysphagia. Future research should compare buccal spray VD3 to intramuscular injections and confirm these findings in well-designed trials.

Conflict of Interest
There is no conflict of interest