



Effectiveness of the new IVACG early high-dose vitamin A supplementation scheme compared to the standard WHO protocol: A randomized controlled trial in Gambian mothers and infants

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Abstract

Background: Vitamin A supplementation improves childhood mortality by postulated effects on mucosal integrity and systemic immunity. Most developing countries have adopted the WHO standard vit. A dosing schedule. In 2002 the International Vitamin A Consultative Group (IVACG) Anney Accord recommended a new early-high dose regime for mothers and infants but this has not been tested. **Aim:** To compare the benefits of the proposed high dose (HD) regimen vs WHO standard dose (SD) on multiple health outcomes in an area of moderate vitamin A deficiency in rural Gambia.

Methods: We randomly assigned 220 mother-infant pairs to a double-blind trial comparing the IVACG early high-dose protocol against the standard WHO dose. The primary outcome measures were: plasma vit. A of mothers (2m postpartum) and infants (in cord blood, 2m, 5m, 9m and 12m); infant *H. pylori* infection and gut epithelial integrity at 2m, 5m, 9m and 12m; maternal and infant *S. pneumoniae* carriage at 2m, 5m and 12m. **Secondary outcomes:** breast-milk vit. A and mammary epithelial integrity monthly for 6m; monthly growth and twice weekly morbidity for months; and acute phase proteins of AGP and CRP in cord blood and at 2m (mothers and infants), 5m, 9m, and 12m (infants only). The trial is registered as ISRCTN 98554309.

Results: One hundred and ninety seven infants completed follow up to 12 months (99 HD, 98 SD). There was no evidence of adverse events at dosing in either group. No difference could be detected in the primary outcomes: HD vs SD differences (95% CI) maternal vit. A at 2m +0.02µmol/l (-0.10, 0.15), infant vit A at 5m +0.01µmol/l (-0.08), *H. pylori* infection at 12m -0.3% (-14.7, 14.2), maternal pneumococcal carriage at 12m -2.0% (-13.7, 9.7), infant pneumococcal carriage at 12m 14.1% (-15.8, 7.6) infant gut mucosal damage at 12m +5.2% (-8.7, 19.2) there were more clinic attendances by the HD group in the first 6m of life (P=0.018). Other secondary outcomes did not differ. Vit. A status gradually improved in infants from both groups; from 60% deficiency in cord blood to 20% deficiency at 12m.

Conclusion: These results do not support the proposal to increase the existing WHO standard dosing schedule for vit. A deficiency in areas of moderate vit. A deficiency.

Introduction

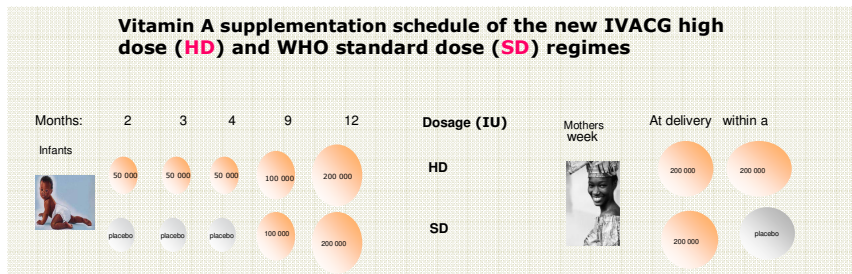
Vitamin A supplementation of mothers and children using the standard WHO protocol (SD) reduces mortality by postulated effects on mucosal integrity and systemic immunity and has been adopted as a national policy in most developing countries. However the benefits of early post-partum supplementation of young infant has been controversial. In 2002 the International Vitamin A Consultative Group (IVACG) Anney Accord recommended a new early-high dose (HD) regime, which has not been tested, for mothers and infants.

Objective

We aim to compare the benefits of the proposed (HD) vs (SD) regimen on multiple health outcomes in an area of moderate vitamin A deficiency in rural Gambia.

Method

We conducted a RCT in the Gambia, an area of moderate vit. A deficiency, among 220 mother-infant pairs studied from birth through to 12 months to compare the benefits of the HD vs SD.



Primary outcomes: plasma vit A of mothers (2m postpartum); infant plasma vit. A, infant epithelial integrity and *H. pylori* infection at (2m, 5m, 9m, and 12m); maternal and infant nasal *S. pneumoniae* carriage at 2m, 5m, and 12m. **Secondary outcomes:** breast milk vitamin A, mammary epithelial integrity, growth, morbidity and acute phase proteins of CRP and AGP at follow up (see Table 1).

Table 1. Tests and follow up schedule

	Time	Samples
Mothers	At Delivery	10ml cord blood
	2 months	5ml venous blood
	Monthly to 6 months	10 ml breast milk
Mother & Infants	At birth, 2, 5, & 12 months	Nasal swab
Infants	At birth	5 ml cord blood
	At 2, 5, 9 and 12 months	3.5 ml venous blood
	At 2, 5, 7, 9 and 12 months	LMR, UBT
	Monthly up to 12 months	Anthropometry
	Twice-weekly for 12 months	morbidity

LMR = Lactulose : Mannitol Ratio; UBT = Urea Breath Test

Table 3. Proportion of clinic attendances in both groups compared

Age (Mo)	HD	SD	P-value
1 - 3	24	13	0.049
4 - 6	29	15	0.018
7 - 9	31	29	0.56
10 - 12	22	16	0.29
1 - 12	49	32	0.016

Results

One hundred and ninety-seven infants completed follow up to 12 months (99 HD, 98 SD). There was no evidence of adverse events at dosing in either group. No difference could be detected in the primary outcomes except maternal *S. pneumoniae* carriage at 2m, where mothers in the HD group had significantly higher carriage than those in the SD group (33.7% vs 15.3%; P = 0.003). Infants in the HD group had significantly higher proportion of clinic attendances in the first 6 months of life than those in the SD group (29% vs 15%; p = 0.018). Other secondary outcomes did not differ.

	Plasma level							
	Retinol (µmol/l) ¹				Proportion deficient ²			
	n	High Dose	n	Standard Dose	95% CI for difference ³	High Dose	Standard Dose	95% CI for difference ⁴
Infants								
Cord Bld	92	0.69 (0.20)	92	0.67 (0.21)	0.02 (-0.04, 0.08)	55.4%	60.9%	-5.5 (-20.0%, 9.1%)
Month 2	63	0.74 (0.21)	71	0.72 (0.20)	0.02 (-0.06, 0.09)	44.4%	43.7%	0.7 (-16.4%, 18.0%)
Month 5	72	0.84 (0.21)	76	0.83 (0.21)	0.01 (-0.06, 0.08)	27.8%	31.6%	-3.8 (-18.8%, 11.2%)
Month 9	78	0.85 (0.23)	75	0.85 (0.22)	0.00 (-0.07, 0.08)	25.6%	30.7%	-5.1 (-19.6%, 9.5%)
Month 12	64	0.87 (0.25)	64	0.94 (0.28)	0.07 (-0.17, 0.02)	23.4%	18.8%	4.6 (-9.7%, 19.1%)
Mothers								
Month 2	96	1.43 (0.44)	97	1.41 (0.40)	0.02 (-0.10, 0.02)	4.2%	4.1%	0.1 (-5.7%, 5.8%)
	Breast milk levels							
	Retinol (µmol/l) ¹				Proportion deficient ⁵			
	n	High Dose	n	Standard Dose	95% CI for difference ³	High Dose	Standard Dose	95% CI for difference ⁴
Month 1	94	2.01 (1.07)	93	1.86 (0.81)	0.15 (-0.13, 0.43)	12.8%	15.1%	-2.3 (-12.4%, 7.8%)
Month 2	96	1.69 (0.79)	95	1.67 (0.67)	0.02 (-0.19, 0.24)	17.7%	18.9%	-1.2 (-12.4%, 10.0%)
Month 3	94	1.68 (0.79)	96	1.74 (0.78)	-0.06 (-0.29, 0.16)	23.4%	18.8%	4.6 (-7.2%, 16.5%)
Month 4	95	1.54 (0.75)	97	1.55 (0.84)	-0.01 (-0.24, 0.21)	21.1%	32.0%	-10.9 (-23.5%, 1.7%)
Month 5	96	1.50 (0.88)	96	1.47 (0.85)	0.03 (-0.21, 0.27)	28.1%	37.5%	9.4 (-22.9%, 4.1%)
Month 6	96	1.56 (0.84)	96	1.47 (0.71)	0.09 (-0.14, 0.31)	27.1%	33.3%	-6.2 (-19.5%, 7.0%)

¹, mean (sd); ², cut-off for VAD = 0.7µmol/l; ³, differences assessed by one way ANOVA against treatment; ⁴, differences assessed by Chi-square test; ⁵, cut-off = 1.05 µmol/l

Table 2. Plasma and breast-milk retinol levels and proportions of subjects recorded as deficient

Conclusion: These results do not support the proposal to increase the current WHO standard vit. A dosing schedule in areas of moderate vit. A deficiency. Further testing in areas of severe deficiency may be warranted, but caution is urged since other trials have indicated possible adverse effects of high doses and potential interaction with EPI vaccines. Progress in determining the optimum vit. A dosing requires a detailed understanding of the mechanism by which it reduces mortality.