these additional cadre of worker also will need clarity before creating an additional cadre of AWWs.

Thus, a package which caters to all these factors needs to be developed and be reciprocated in various settings with the involvement of both governmental and non-governmental organizations to generate better evidence.

Conclusions

Chronic malnutrition, which is a result of long-term energy/calorie and protein deficit leads to stunting. From the time of conception to the second birthday of the child, also known as the first 1000 days of life, is the most vulnerable period for growth and development. This period determines the future health status of the child. Hence, we need interventions targeting this crucial period and in line with the findings of the above-mentioned study, the recommendation for an additional worker to supplement or augment the service package being provided at the community, appears to be feasible and may also reduce the burden on existing AWWs; however, strengthening the existing nutrition-related services with integrated focus of both nutrition-specific and -sensitive interventions (with community participation by including beneficiaries, schools, non-governmental organizations, mahila samitis, self-help groups, de-addiction centres, village health committees, ASHAs, ANMs, AWWs) in the entire duration of the first 1000 days of life seems to be a better approach for studying the effect of these interventions on child's growth.

Conflicts of interest. None declared

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Effectiveness of quarter standard-dose combination therapy for initial management of hypertension

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SUMMARY

In this placebo-controlled, double-blind, cross-over trial, 18 treatment-naïve adults with hypertension were recruited and given either

'Quadpill' or placebo for 4 weeks, followed by a washout period of 2 weeks. The two groups were then crossed over to receive the other intervention for 4 weeks.[1] The eligible participants were adults aged 18 years and older with office systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg or both, on two readings on separate days; baseline ambulatory SBP >135 mmHg or DBP >85 mmHg or both; and not taking any blood pressure drugs. Individuals with known definite contraindication to any component of Quadpill; with severe/accelerated hypertension; when in the clinician's judgement a change in the current treatment would risk their life; who were pregnant; with medical illness with life expectancy <3 months were excluded from the study. The intervention, referred to as the 'Quadpill', was a quarter-standard dose combination, containing irbesartan (37.5 mg), amlodipine (1.25 mg), hydrochlorothiazide (6.25 mg) and atenolol (12.5 mg), which were the quarter doses of the standard antihypertensive medications commonly prescribed in the study area. The primary outcome measure was a reduction in mean 24-hour SBP using ambulatory blood pressure monitoring following 4 weeks of Quadpill therapy. The secondary outcome measures were a reduction in mean 24-hour DBP using ambulatory blood pressure monitoring following 4 weeks of Quadpill therapy; reduction in office blood pressures; proportion of study participants who achieved controlled blood pressure following Quadpill therapy; adverse events and change in laboratory parameters. Blood pressures were measured at four-time points; at baseline, at the end of first intervention after 4 weeks, after a washout period of 2 weeks and after the second intervention period of 4 weeks. All the analyses were intention to treat (ITT).

It was reported that there was a difference of 18.7 (95% CI 14.3–23.0) and 14.2 (95% CI 11.5–16.9) mmHg in the mean 24-hour SBP and DBP, respectively, following 4 weeks of Quadpill therapy. Controlled ambulatory blood pressure (blood pressure <135/85 mmHg) was achieved in 83% of the study participants following Quadpill therapy when compared to 39% of participants in the placebo group (risk ratio [RR] 2.14, 95% CI 1.25–3.65; p=0.0053). The office blood pressures were controlled (<140/90 mmHg) for all participants after Quadpill therapy compared with 33% in the placebo group (RR 3.01, 95% CI 1.54–5.89; p=0.0013). It was reported that treatment compliance was better in the intervention group and was measured using 'number of capsules missed in the last 1 week' and it was seen that the number of capsules missed was higher in the placebo group than in the intervention group (0.3 *v*. 0.2). It was unclear if compliance was self-reported or by observation of returned empty blister packs. The intervention was well tolerated, and there were no life-threatening adverse effects during the study. However, there was a significant increase in the blood levels of glucose (0.2 mmol/L, 95% CI 0.02–0.4; p=0.04), urate (0.03 mmol/L, 0.01–0.04; p=0.003) and creatinine (4.4 mmol/L, 0.9–7.8, p=0.02) following 4 weeks of Quadpill therapy. It was concluded that quarter dose therapy could be additive across classes of antihypertensive medication and can clinically reduce blood pressure. In addition, authors have also presented a systematic review by including similar studies done using quarter doses of antihypertensives against placebo in the current paper. It was reported that when one drug with quarter standard dose was tested against placebo (36 studies), it caused a mean (95% CI) reduction of 4.7 (3.9–5.4) mmHg in SBP and 2.4 (1.9–2.8) mmHg in DBP. When two drugs were used (6 studies), it caused a reduction of 6.7 (4.8–8.6) mmHg in SBP and 4.4 (3.3–5.5) mmHg in DBP.

COMMENT

This study was one of the first to report the efficacy of quarter-dose quadruple combination therapy for reduction of blood pressure in the initial management of hypertension. The novel concept of quarter-dose antihypertensive combination therapy for the initial treatment of hypertension may be useful for effective control of non-communicable diseases (NCDs), particularly hypertension. Due to increasing prevalence and higher development of complications such as stroke, new concepts of preventive pharmacotherapy have initiated many studies which promote the administration of antihypertensive therapy among newly diagnosed uncomplicated cases of hypertension. The burden of NCDs in developing countries including India has been on the rise affecting all strata and this also has led to a rise in the number of patients with poor blood pressure control and complications.[2]

The major reasons proposed for the poor control of blood pressure among those with hypertension have been broadly categorized into those caused by the provider and those by the patient. Provider-related causes mainly contributed by therapeutic inertia.[3,4] There is a need to diagnose NCDs early and treat them effectively to prevent complications and reduce morbidity and mortality. Quarter standard-dose combination therapy also improves compliance and causes fewer side-effects as compared to their individual standard doses. However, there is a need for caution as a sudden fall of blood pressure, especially among the vulnerable population, for example, elderly could lead to more harm than benefit.

Certain methodological issues need to be kept in mind while interpreting the results of this study. The Quadpill could have been more effectively proved to be useful in the clinical setting if its effect and side-effects profile were compared with the standard treatment instead of the placebo. Quadpill might have been compared with placebo to study its true effect, but still, its usefulness in the clinical scenario needs to be established by comparing it with standard therapy. However, it is unethical to withhold standard treatment from a patient once diagnosed with a disease/condition. In spite of it being a crossover study, the patients after diagnosis have not received treatment for at least 6 weeks following enrolment. Ambulatory blood pressure measurements were used and this ensured provision of more accurate readings. ITT analysis was performed. However, it was not mentioned whether the two participants who withdrew themselves from the study were included in the analyses. Their exclusion would require per-protocol analyses instead of ITT analyses. The mean 24-hour DBP using ambulatory blood pressure monitoring following 4 weeks of Quadpill therapy could have been included as a primary outcome.

All participants were educated on healthy lifestyle options available as per their current guidelines.[5] These included dietary modifications with low salt intake <4 g/day, at least 30 minutes of moderate-intensity physical activity on most days of the week, smoking/tobacco cessation and limited alcohol intake, reduction of body weight. This could have led to an additive effect on the lowering of blood pressure; however, the placebo group did not demonstrate any significant reduction in mean blood pressures. Non-pharmacological interventions may take a longer time to show effects unlike pharmacological interventions and still need attention. However, we fail to understand how the placebo group managed to experience a control in ambulatory blood pressure (39%) and office blood pressure (33%) despite not much change in the mean blood pressures. It is unlikely that lifestyle modifications could have played some role in controlling blood pressure with immediate effect. The calculated sample size could not be achieved in the study; thus, one would analyse the results with caution assuming the internal validity of the study would have been affected, which, however, has been acknowledged by the authors and was taken care of in the analysis by the Kenward

and Roger method. However, the small variance and high mean difference of blood pressure between the two groups have managed to maintain the internal validity of the study. There was a high non-participation rate in the study, 40% of the screened sample refused to participate in the trial. Thus, the results from the study cannot be generalized to the study population. The study included treatment-naïve newly diagnosed patients with hypertension who were not allergic to any specific component in the Quadpill drug. However, contraindication or allergy to even one component of the Quadpill drug challenges the use of the drug more commonly. The occurrence of adverse effects was compared between the Quadpill and the placebo groups. However, if the Quadpill were to be compared with the standard therapy and the adverse effects were studied, we could have had a better understanding of the effects of Quadpill. There was a significant difference in the levels of urea, creatinine and glucose levels in the intervention group, which cannot be ignored. Looking at the side-effects following quarter-dose combination therapy, one may assume that side-effects may be higher among those who consume the standard full-dose therapy. More studies are required comparing combination therapy against standard therapy, with and without non-pharmacological interventions for better understanding of the pharmacodynamics and its clinical significance. The study has administered Quadpill for 4 weeks which may not be sufficient to significantly affect the blood parameters and long-term studies are required. The authors discuss that this study along with the help of systematic review and meta-analysis concluded that quarter-dose combination therapy was effective in controlling blood pressure, but they could have discussed in detail other factors such as lifestyle and dietary changes.

This study addresses most of the limitations in a similar study done in Dublin, Ireland (2007), among 110 treatment-naïve patients with hypertension divided into five groups where one received the quadruple therapy (n=22) for 4 weeks and were compared with individual drugs in parallel. The reduction in mean arterial pressure with combination therapy was 19 mmHg.[6] Previous reviews and meta-analyses done on this topic have also claimed that combination therapies have been shown to be more efficacious in significantly reducing blood pressure.[7,8] Polypill may prove to be effective, but the double-edged effects may require caution before administration. Quarter standard-dose combination therapy could be a challenge for its use in the initial management of hypertension as we do not have sufficient data on the proportion of newly diagnosed hypertensive patients currently on standard treatment who are non-responsive, refractory or worsening with treatment. We require further trials among a larger number of patients and also there is a need to study long-term effects of the drug and implications of sudden reduction of blood pressure among newly diagnosed individuals with hypertension.

Conflicts of interest. None declared

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