

## COMMENT

Pancreatic leak and fistula continue to be the Achilles' heel of pancreatic resection despite many advances in the technique. These result in the formation of intra-abdominal abscesses, and may even cause haemorrhage. Prevention of pancreatic leak has been the Holy Grail for surgeons the world over. Numerous techniques have been devised in a futile bid to decrease or eliminate pancreatic leakage, with variable results.<sup>1</sup> The somatostatin analogue, octreotide was used a decade ago in an attempt to inhibit pancreatic secretion and thereby decrease leak and fistula. Whereas results from Europe showed some benefit, the results from the USA did not, and the use of octreotide is not widely recommended.<sup>2,3</sup> It is possible that the mixed results with octreotide were due to a lack of standardization of what constituted pancreatic leakage, which is now available with the International Study Group for Pancreatic Fistula (ISGPF) system.<sup>4</sup>

Pasireotide is a new analogue of somatostatin and is an orphan drug developed for the treatment of pituitary lesions. It has a considerably longer duration of action (half-life of 11 hours *v.* 2 hours of octreotide), and its affinity to the somatostatin receptor is higher (it binds to somatostatin receptor types 1, 2, 3 and 5 with affinity of 5 to 40 times as octreotide; the latter binds only to receptors 2 and 5).<sup>5</sup>

This unique study may well be a landmark publication in the search for preventive solutions to postoperative pancreatic leakage. However, there are concerns, which may be grouped into issues of applicability and efficacy. Dose-limiting nausea was observed in 17% of patients in the pasireotide group, and the drug was not used if blood sugar levels were >250 mg/dl or if the QT interval was abnormal. Over 50 patients in each arm were deemed ineligible. Many patients who undergo pancreatic resection either have diabetes or may have associated cardiac problems, and this raises the issue of how applicable this drug is in all patients eligible for pancreatic resection. The completion of pasireotide therapy occurred in only 75.7% and thus a quarter of patients did not receive the full quota of the drug. It could be argued, however, that the results in the pasireotide were better despite this shortcoming.

Outcomes following DP and PD are substantially different. In PD there is a pancreaticoenteric anastomosis with issues of postoperative feeding, whereas the pure pancreatic leak following DP is easier to manage. Further, first, routine peritoneal drains are placed after resection in most if not all centres that perform pancreatic surgery around the world. However, the authors of the

paper have not performed routine drainage, and this has prevented application of the ISGPF grading system for pancreatic fistula in assessing the results; second, a variety of techniques have been used in closure of the pancreatic stump or in pancreaticoenteric drainage and they may impact on the outcomes of the study; third, ductal dilatation is only one factor which affects outcome after surgery. The soft nature of the gland, friability and fat content have all been implicated, and since the prevalence of these characteristics has not been studied, there is a possibility that the final outcome may not be applicable to the high-risk pancreatic anastomosis.<sup>6</sup>

Regardless of these limitations, the observations represent an important step forward. It remains for future trials to substantiate and reproduce the results of this trial. Two questions arise: (i) will pasireotide fulfil this early promise, and (ii) in view of the high cost of pasireotide, is it a good time to resurrect octreotide and study its efficacy one more time?

Octreotide was evaluated in the pre-ISGPF era and heterogeneity in trial design and lack of definite end-point definition may have resulted in studies failing to show efficacy.

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## Is double-fortified salt a panacea for iron-deficiency anaemia in India?

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Science, Pennsylvania State University, University Park, Pennsylvania, USA; Micronutrient Initiative and International Development Research Centre, Ottawa, Ontario, Canada; Mathile Institute for the Advancement of Human Nutrition, Dayton, Ohio, USA.) Double-fortified salt is efficacious in improving indicators of iron deficiency in female Indian tea pickers. *J Nutr* 2014;**144**:957–64.

## SUMMARY

This study reports the findings of a double-blind randomized controlled trial conducted to assess the efficacy of double-fortified salt (DFS) (iron and iodine) in improving the iron status of women. It was done

at Panighatta tea estate in Darjeeling district, West Bengal, India and included women workers between 18 and 55 years of age. The iron status was assessed by levels of haemoglobin, serum ferritin and soluble transferrin receptor (sTfR). The required sample size for the study was 164, which was based on the assumption of detection of increase of serum ferritin level from 15 µg/L to 26 µg/L. A total of 498 women were screened, of which 245 women were enrolled in the study.

The study participants were stratified into those with mild-to-moderate anaemia and those who did not have anaemia. They were randomized to receive either DFS (intervention group) or iodized salt (control group). Thirty-three women were lost to follow-up during the 10 months of the study. The intervention group received DFS containing 47 mg of potassium iodate and 3300 mg of microencapsulated ferrous fumarate (1100 mg elemental iron) per kg of salt. The control group consumed only iodized salt (with added sodium fumarate to give it an appearance similar to DFS). Allocation concealment and blinding was done by using four-colour coded salt bags (two of them containing DFS and two iodized salt) whose composition was known only to the manufacturer. No other salt was sold in the community during the intervention period. Haemoglobin, mean corpuscular volume (MCV), serum ferritin, sTfR, C-reactive protein (CRP), alpha-1 acid glycoprotein (AGP), vitamin B12 and serum folate were measured at baseline and end-line using venous blood sample. Body iron was derived using the adjusted values of sTfR and serum ferritin. Salt consumption was measured by 24-hour dietary recall method and salt disappearance method was used for total household salt use.

There was no significant difference between the intervention and the control groups at baseline. Fifty-three per cent of women had anaemia at baseline, of these 23% had iron-deficiency anaemia (IDA). The mean (SD) daily estimated consumption of elemental iron was 8.6 (5.7) mg. The mean daily estimated salt consumption by the participants or individuals in households did not differ significantly between the two groups. There was significant improvement in the prevalence of iron deficiency and iron depletion in the DFS group compared to the control group (serum ferritin level <20 µg/L decreased from 45% to 22% in the DFS group and from 44% to 35% in the control group). The difference in the change of levels of haemoglobin, mean serum ferritin, sTfR, body iron between the DFS and control group was 2.7 g/L, 11.6 µg/L, -0.90 mg/L and 1.74 mg/kg, respectively, all of which were significant ( $p < 0.05$ ). The DFS group showed significant improvement in iron status (an increase in haemoglobin level of 2.4 g/L and body iron increase of 1.43 mg/kg) compared to the control group after adjusting for respective baseline iron status measures using General Linear Models (GLM). There was an increase in the level of median urinary iodine in both groups from baseline to the end of the study.

Biological plausibility analyses showed that iron-deficient women had greater improvement in body iron than iron-sufficient women and significant interaction ( $p = 0.02$ ) was observed between the baseline iron status and the improvement in iron status. A dose-response gradient was seen in the improvement of iron status with increase in the amount of DFS consumption. The study showed that DFS improved the levels of haemoglobin, ferritin, sTfR and body iron concentrations in women over a period of 10 months.

#### COMMENT

IDA and its association with child and maternal mortality and morbidity, preterm labour, low birth-weight, cognition and work capacity, warrants a multi-pronged approach to address the situation. IDA leads to a loss of 25 million disability-adjusted life-years (DALYs), accounting for 2.4% of the total DALYs lost worldwide.<sup>1</sup> IDA leads to a loss of 4% of gross domestic product (GDP) in developing countries, thereby impeding social and economic development in affected countries.<sup>1</sup>

This is one of the few studies reporting efficacy of DFS (iron and iodine) consumption in improving iron status (haemoglobin, serum ferritin, sTfR and body iron) among women. Two other studies, one from India<sup>2</sup> and the other from Ghana<sup>3</sup> have reported a positive impact of DFS on anaemia but did not assess other iron status parameters. Few other studies have studied the impact of DFS on iron status among children and have reported similar findings.<sup>4</sup> The limitations of this study included per protocol analyses instead of the more robust intention-to-treat analysis. There was a potential for contamination across the control and intervention arms, as the sharing of lunch was common among the tea estate workers. However, contamination will only make the findings of the study more conservative and if we were to remove the effect of contamination, the difference between the two groups will be even greater. The 24-hour recall method and disappearance method for assessment of salt intake in the study is prone to overestimation. However, as this overestimation is unlikely to be differential in the control and intervention groups, it did not lead to bias in the study. The gold standard method for salt intake measurement, the 24-hour urinary sodium estimation would have provided more reliable and valid results.

The findings of the study have important implications for India as it has among the highest known burden of anaemia globally; 55.8% of women in the age group of 15–49 years, 24% men, and 70% of children aged 6–59 months being anaemic.<sup>5</sup> Iron supplementation, which has been the mainstay of the national nutritional anaemia prophylaxis programme, has had limited success in addressing IDA.<sup>6,7</sup> This is primarily because of frequent disruption in the supply chain of iron tablets and low compliance to iron supplementation. Iron fortification of salt and other food items such as flour can be an alternative strategy to address IDA in India. Salt is produced in a few centres in India and with its low cost, wide availability and regular consumption in constant amount makes it an ideal vehicle for fortification.

India has pioneered the scientific technology related to DFS, with one of the formulations being developed indigenously.<sup>8</sup> Recently, the Government of India has issued directives for mandatory use of DFS in national food and nutrition programmes including the Integrated Child Development Scheme (ICDS) and the Mid-Day meal programmes. The use of DFS as a programme intervention can be modelled on the success of the iodized salt programme in India. However, unlike iodized salt, change in organoleptic properties, high fortificant-to-vehicle ratio and a shorter shelf-life of DFS make the scaling up of DFS a more challenging proposition. Also, while all grades (quality) of salt can be iodized, DFS requires high-quality salt (NaCl content >99%). This increases the costs of DFS and has logistic issues in terms of limited capacity of the salt industry in India to produce 99% NaCl grade salt.

There is a need for more studies to assess the effectiveness of DFS in different settings and age groups. There is also a need to build capacity of the salt industry in India to produce high-quality salt and to manufacture DFS. DFS alone may not suffice to address the burden of IDA, but it has a role along with proven interventions such as iron supplementation and diet diversification. The implementation of DFS programme also has to be studied for its impact on universal salt iodization and the salt reduction programme, which are important public health issues in India.

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