NFI BULLETIN
Bulletin of the Nutrition Foundation of India
October 1991 Volume 12 Number 4

Prevention And Control Of Goitre

Demerits Of Iodised Oil Injections

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Iodised oil injection as an alternative strategy for the prevention of endemic goitre was introduced by McCullagh in New Guinea in 1957. He showed[4,7] that the injection of 4 ml of iodised oil, containing 2.15 gram of elemental iodine, ensured the correction of severe iodine deficiency for as long as 4.5 years and reduced the incidence of goitre. Since endemic populations in New Guinea belonged to far-flung and isolated terrains, salt iodation as a means of iodine prophylaxis was thought to be logistically difficult. Therefore, a large-scale iodised oil injection prophylaxis (IOP) was mounted, involving thousands of injections. In this presentation, an attempt will be made to review relevant data on the merits of this approach.

PHARMACOLOGY AND TOXICOLOGY OF OIL

The most widely advocated and used iodised oil preparation is the Lipiodol brand of iodised poppy-seed oil put out by Guebert, Paris. It is a clear pale yellow fluid which is reported to have a specific gravity of 1.2080 and viscosity of 0.5 to 1.0 poise at 15°C[8]. It contains 37 to 38 percent iodine (wt/vol)[8,17]. Though the iodine in Lipiodol is reported to be in covalent linkage[8], in our experience, on opening the 10 ml vials and exposing to atmosphere, the solution soon turns deep brown, due presumably to the release of free iodine. The chemical nature of iodised oil is believed to be variously iodinated ethyl esters of fatty acids that constitute poppy-seed oil[8].

Virtually nothing is reported regarding the bio-chemical specificity of the different iodinated fatty acids and other compounds that constitute Lipiodol. Also, virtually no data are available on animal toxicological studies (acute and chronic) involving Lipiodol. Specific questions relating to the acute and chronic toxic effects, as well as the teratogenic potential of hetro-poly iodised fatty acids, cannot be answered without carefully done animal toxicological studies. Such questions are of direct relevance to the IOP programme, in view of the recent suggestion that iodised oil be introduced as a component of the maternal and child health programme, involving administration to pregnant mothers and new borns!

Much of the published information on the pharmacology of Lipiodol relates to its pharmaco-kinetics. The most significant contribution in this regard has been that of Pretell *et al*[17]. Using I-131 labelled Lipiodol, Pretell demonstrated that 99.3 percent of I-131 was covalently bound to the oil. However, when I-131 labelled oil was incubated with human serum in 1:100 dilution at 37°C, progressive deiodination was demonstrable. By this process, as much as 13.2 percent of I-131 was deiodinated by 15 hours of incubation. Their studies also showed that during the same period as much as 6.7 percent iodinated Lipiodol was incorporated to serum proteins or serum lipoproteins.

Studies in rats given 1/M Lipiodol I-131 show that as much as 87 percent of radioactivity was retained at the 1/M site 23 days post-injection. During the same period, 8 percent radioactive I-131 appeared in urine and 0.2 percent was concentrated in the thyroid. These studies also showed that besides thyroid, which concentrates the maximum proportion of released iodine, other tissues such as adipose tissue, kidney, lymph nodes, salivary gland, lungs and liver also take up and retain the released iodine, presumably in the form of iodated fatty acids. As fatty acids get incorporated both in depot fats and membrane structures in the body, these observations are of importance, particularly from the point of view of toxicity to the developing child in utero.

Malamos *et al*[13] using I-131 labelled Lipiodol, followed the disappearance of I-131 from injection sites. According to their computations, the biological half life of 1 ml injected Lipiodol was ~70 days. The disappearance was found to be linear over this period of time. Malamos *et al* also found 1 percent of the dose of administered I-131 in the thyroid by day four, and as much of 30 percent was absorbed from the injection site by day 28 post-injection.

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The type of metabolic transformation that occurs to injected iodised oil in the body is not known. In what form it is dispersed from the injection site is also not known.

The pattern of urinary iodine excretion (UIE) by subjects who received IOP has been studied by more than one author. One of the earliest studies in this regard was reported by Pretell on the basis of measurements done in two subjects[17]. One of them received 0.2 ml Lipiodol while the other received 2.0 ml 1/m. Pretell found identical linear slopes of I-131 excretion in these two subjects, with half-lives of 5.6 months. However, in this study, the first point of UIE estimation done following IOP was six months post-injection and therefore no quantitative data was available on early phase iodine excretion following IOP. In a subsequent study[17], the same author reported a rapid increase in UIE from control values of 40 µg/24 hour to almost 10 mg/24 hour, which then declined to less than half of this value in day 30 post-injection. UIE subsequently stabilised to a slow exponential rate of excretion; keeping up satisfactory UIE levels for as long as 60 months post-injection (Figure 1). Thus a close follow-up study on the pattern of UIE following IOP showed a pattern of multiple exponential excretion with an early phase of massive rapid iodine excretion and a late phase of slow and minimal iodine excretion. In a study done on 10 goitrous subjects (Figure 2) who received 1 ml iodised oil injection at AIIMS, we could demonstrate high levels of UIE ranging up to 10 mg/24 hour for as long as four to six weeks with subsequent decline to more physiological levels of UIE daily[11]. Similar findings have been reported by Thilly *et al* from Zaire[18].

Pretell[17] has analysed the chemical nature of iodine excreted in the urine following IOP and has concluded that 70-80 percent is accounted for by inorganic iodine and the remaining as organic iodine. The nature of organic iodine excreted in the urine following IOP is not clear. *There is, thus, consensus in literature that following a 1 ml injection of Lipiodol, pharmacological levels of inorganic iodine are excreted daily by the subjects for as long as six to 12 weeks.*

EFFICACY OF IOP

Ever since its successful initial trial in New Guinea, millions of iodised oil injections have been administered as prophylactic measure to prevent endemic goitre and cretinism in developing countries such as Indonesia, Nepal, Ecuador, Peru, Argentina and Zaire. There have been studies to assess the efficacy of this measure, mainly from the point of view of preventing goitre and cretinism prevalence.

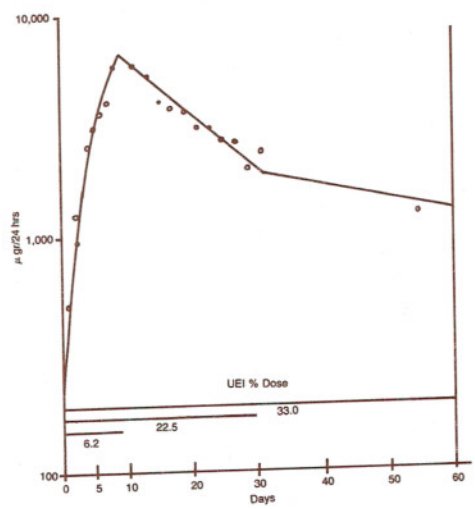
The impact of IOP in reducing the prevalence of endemic goitre and improving iodine and thyroid status of people in the various endemics of the three continents where it has been used has been impressive. However, available data do not show that IOP has eradicated endemic goitre or cretinism from any area of prophylaxis. Also, limited studies on acute effects of IOP in the immediate post injection phase show that in a significant number of subjects, an increase in TSH levels and a decline in T_4 levels occurred[5]. These, however, may be transient. Most of the studies report an absence of any significant toxic complications following IOP. However, there is paucity of any systematic studies to underscore this 'impression'.

IOP AND PREVENTION OF ENDEMIC CRETINISM

Though endemic goitre is etiologically linked with nutritional iodine deficiency in most of the endemics of the world, the relationship between iodine deficiency and endemic cretinism was not clear till the studies of Pharoah and Hetzel in the Jimi River district of western New Guinea in 1966[15]. The results of this study, involving a controlled trial of iodised oil injection to prospective mothers, are summarised in Table 1. Based on these results, Pharoah and Hetzel concluded that "intra-muscular injection of iodised oil was effective in the prevention of endemic cretinism, but that to be effective it had to be given prior to conception"[15].

Subsequent to this, Flerro-Benitez

Figure 1
E.A. Pretell's study



Early urinary losses of iodine following the injection of 1.0 ml (475 mg I) of iodised oil.

Figure 2
Urinary Iodine Excretion (UIE) — AIIMS study

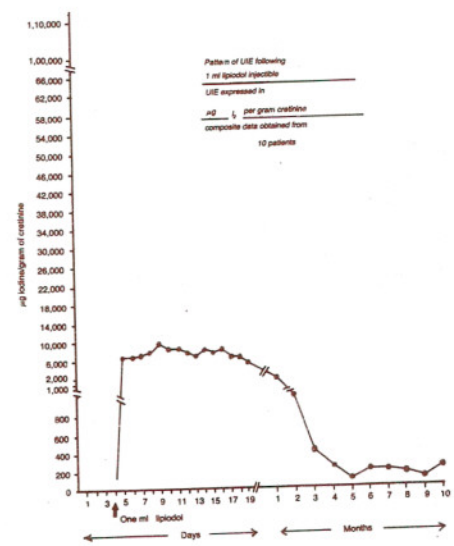


Table 1
The New Guinea study

Maternal treatment	Total new births	No. of children	No. of deaths recorded	No. of cretinism detected
Iodised 1/M	498	412	66	7 *
Untreated	534	406	97	26

** In six of seven cretins detected, the mother received IOP intrapregnancy.*

et al published the results of a prospective study to assess the impact of maternal IOP (prenatally or/and during pregnancy) on the mental development of children born to such mothers. A control village without IOP was also simultaneously studied. The results of this controlled prospective study showed that correction of iodine deficiency by IOP after the fifth month of pregnancy had little or no effect in preventing mental retardation in offspring, whereas IOP before the onset of pregnancy improved the mental status of children[6].

A similar prospective study for five years after IOP, done in a Peruvian endemic by Pretell *et al*, to assess the impact of IOP in prevention of cretinism and related mental subnormality provided inconclusive results. However, there was a clear tendency to higher IQs among children born to mothers who had iodised oil before pregnancy. The authors concluded that more careful studies are required to firmly establish the role of IOP in preventing cretinism[17].

From the above studies, the striking fact that clearly emerges is that intrapregnancy injections of iodised oil do not prevent cretinism or mental subnormality among children born to iodine deficient mothers. On the basis of this observation, Pharoah and Hetzel postulated that elemental iodine may be required for early foetal brain development even before foetal thyroid develops and that early foetal iodine deficiency may be important in the pathogenesis of neurological defects in endemic cretinism. However, this hypothesis, when tested by Hetzel by appropriate experimental studies in sheep, could not be substantiated. It is now fairly well established that endemic cretinism can be prevented by iodised oil prophylaxis only if given before pregnancy.

NEONATAL CHEMICAL HYPOTHYROIDISM (NCH) — RELATIVE MERITS OF IOP AND ISP

High incidences of NCH (T_4 < 3 µg/dL and TSH > 50 µU/mL) have been reported from endemic goitrous regions of India, Zaire and Sicily. Based on current understanding of the role of thyroxine in foetal and neonatal brain development in man, the high incidence of NCH demonstrated in endemic areas would have a serious adverse consequence on the brain development of emerging generations. The large number of cretinous and sub-cretinous defectives seen in seriously iodine deficient endemias can therefore be regarded as a phenomenon related to the high incidence of foetal and neonatal hypothyroidism in such areas. Data relating to prevalence of neurological defects characteristic of endemic cretinism to incidence of NCH have been published from India[10].

Other socio-economic concomittants of serious goitre endemias such as PEM and dietary goitrogen ingestion may also be contributing to the pathogenesis of neurological defects associated with endemic iodine deficiency. On the basis of these, NCH has been recognised as an important constituent of the syndrome of Iodine Deficiency Disorders[9]. Consequently, the prevention of NCH should be a major and fundamental objective of iodine prophylaxis. Screening for NCH thus becomes an important measure to assess brain damage risk in goitre endemias, as well as in evaluating the impact of iodine prophylactic programmes.

IOP: In a preliminary study done in Zaire to assess the efficacy of maternal iodised oil injection in improving neonatal thyroid status, Thilly *et al* had reported success in 1979[18]. In 1982-83, when we found very high incidence of NCH in the Tarai districts of Uttar Pradesh, realising the serious nature of endemic iodine deficiency there, we had written a proposal to mount a massive IOP programme, specifically targetting women in the reproductive age group and children. In response to this proposal, the authorities of Ministry of Health, Government of India suggested that a pilot study be done in this regard, as an initial step.

Table 2

Incidence of NCH among new borns of mothers given iodised oil and iodised salt prophylaxis during the third trimester — Indian study

Clinic group	No. of new-borns studied	No. of NCH detected
Babies born in mothers given iodised oil injection in the 3rd trimester	154	16 (11.2%)
Babies born to mothers given iodised salt prophylaxis during 3rd trimester	140	2 (1.4%)

Therefore, with support from UNICEF, we initiated a pilot IOP programme in some PHCs of the Gonda and Deoria districts of U.P. in 1983. The results of the follow-up studies of this IOP[1] showed (Table 2) that the majority of injected subjects excreted satisfactory levels of urinary iodine. The breast-milk iodine content of mothers who received IOP during pregnancy was up to four-fold higher than non-injected control mothers from the same area. However, these encouraging results were vitiated by an unexpected finding[11, 12]. When cord-blood hormone levels (T_4 and TSH) were measured among babies born to mothers who received IOP during the second and third trimester of pregnancy, more than 10 percent of the babies were found to be hypothyroid, using the same criteria we used to diagnose NCH in our earlier studies (T_4 <3 µg/dL and TSH > 50 µU/mL in cord-blood). These findings implied inefficacy of intra-pregnancy IOP in preventing high incidence of NCH in goitre endemias.

When these findings were discussed with experts participating in an international meeting on "Thyroid disorders associated with iodine deficiency and excess" at Freiberg, West Germany, the opinion emerged that the phenomenon may well be due to the toxic inhibitory effect of 'excess' iodine released from the depot injection of iodised oil during the early phase of rapid-exponential iodine decay from injection. That there is indeed such an early phase of rapid and excessive iodine release following IOP has been shown by the studies of Pretell[17] as well as by our own studies[12,11] (Figures 1 and 2). Iodine-induced inhibition of stimulated thyroid gland is a well recognised phenomenon for several decades now

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We are grateful to

UNICEF for a matching

grant towards the cost of

this publication.

Reviews and Comments

Prevention And Control Of Goitre

On Iodised Oil Injections

C. Gopalan

In attempting the control of goitre, or indeed of any other major public health problem, we should carefully avoid falling into the trap of opting for technologies which are not sustainable within our own means — technologies for the continued application of which we will have to be forever dependent on external donors. Relatively inexpensive, and proven technologies well within our means, resources and competence, are now available for the elimination of most of our major public health problems.

The inexpensive technology, a time honoured and time-tested one, for the control of goitre, is the iodation of common salt. Programmes for goitre control must squarely and solidly rest on this technology. Unfortunately the implementation of this strategy has been tardy and inefficient. Either the salt is not properly iodated, or adequate amounts of it are not made available in time to the needy populations, or the programme is unfortunately allowed to run into needless controversies such as "universal iodation" versus "iodation limited only to endemic zones". These are deficiencies in implementation and not in the technology; these deficiencies must be resolutely overcome, and should not be allowed to be used as excuses or arguments for an alternative technology.

There is a strong case for the setting up of an empowered National Goitre Commission which can help to achieve inter-sectoral coordination and expeditious implementation of goitre control programmes as a unified operation with the mandate of achieving the eradication of the disease before the turn of this century. This is specially important as new endemic areas seem to be emerging in the irrigated plains of some Asian countries.

Iodised oil injections: Periodic parenteral administration of iodated oil (not presently manufactured in any Asian country) has been suggested as an alternative approach, especially in areas "inaccessible" to common salt.

It is difficult to imagine of any areas in our country which are now "inaccessible" to common salt, but which will become readily "accessible" to iodated oil, to thousands of disposable syringes, and to an army of "injectors"! Apart from the apprehensions in this regard voiced earlier[1] and the increased expense and the unnecessary drain on meagre foreign exchange resources that this approach would inevitably involve, and apart from the valid arguments against this approach ably presented by Kochupillai in the foregoing article, it must also be remembered that we are now facing two major problems which could get compounded to disastrous proportions through the use of the periodic parenteral administration of iodated oil as a large scale public health operation, namely, the problem of AIDS and hepatitis.

There has been a steep rise in the HIV seropositivity rate among drug addicts of North East India during the last two years. Thus the data of the Indian Council of Medical Research show that half the drug users in this region, which is also precisely the area which is highly goitre-endemic, were seropositive in 1990. Those familiar with real-life situations in the field will realise that "disposable" syringes will not be dutifully "disposed"; under the circumstances, the consequences of resorting to a technology which is dependent on repeated injections (using "disposable" syringes) could be disastrous.

Resorting to large-scale iodated oil injections in the present context would involve unnecessary risks which no responsible health administrator in India should take. It will also be unethical on the part of powerful commercial houses of Europe and "international agencies" to push Asian countries into a technology which does not confer any special advantage over the far less expensive and indigenously available technology of salt iodation; and which could eventually also prove disastrous.

Kochupillai points out in the foregoing article that no developed country of