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ORIGINAL ARTICLE

Comparison between liquid and tablet levothyroxine formulations in patients treated through enteral feeding tube

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Abstract
Background The majority of clinicians suggest that enteral feedings should be held 1–2 h prior to and after L-T4 administration despite lack of data for continuous enteral nutrition.
Aim The aim of this study was to: (1) compare the thyroid hormonal profile in patients submitted to L-T4 treatment in tablets or liquid formulation with an enteral feeding tube; (2) evaluate the nursing compliance with the two different formulations.
Subjects and methods 20 euthyroid patients submitted to total laryngectomy and thyroidectomy consecutively started L-T4 treatment in tablets (Group T) or in liquid formulation (Group L) with enteral feeding tube the day after surgery. Tablets were crushed before administration and enteral feeding was stopped for 30 min before and after L-T4 treatment, whereas liquid formulation was placed into the nasoenteric tube immediately. A questionnaire about the preparation and administration of thyroxine replacement therapy was given to the nurses.
Results No difference of TSH, fT4 and fT3 before and after L-T4 treatment was observed among patients of Group L. A slightly serum TSH increase was observed in Group T, but not reaching statistical significance (2.50 ± 1.18 vs 2.94 ± 1.22 mUI/L), whereas no difference in fT4 and fT3 levels was found. Preparation and administration of liquid L-T4 was considered excellent by 12/13 nurses, whereas tablet formulation was considered poor by 10/13.
Conclusions Our data showed that liquid L-T4 formulation can be administered directly through feeding tube with no need for an empty stomach, with a significant improvement in therapy preparation and administration by nurses.

Keywords Levothyroxine · Liquid formulation · Enteral nutrition treatment · L-T4 · Malabsorption

Abbreviations

L-T4	Levothyroxine
TSH	Thyroid stimulating hormone
fT4	Free thyroxine
fT3	Free triiodothyronine
TL	Total laryngectomy

Introduction

Total thyroidectomy is a common surgical practice in patients submitted to total laryngectomy (TL) for many laryngeal cancers [1]. For this reason the occurrence of hypothyroidism after surgical treatment of the laryngo-thyroid region is not surprising [2].

Nutritional support is necessary in more than 90 % of all the patients with head and neck cancer, and enteral nutrition is the most useful mode of alimentation [3]. Levothyroxine (L-T4) is an effective replacement therapy for patients with hypothyroidism, or suppressive therapy after

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surgical removal of thyroid cancer [4, 5]. After oral administration, approximately 60–90 % of an L-T4 dose is absorbed within 3 h of ingestion. Bioavailability studies indicate that levothyroxine is better absorbed when ingested in the fasting state than when administered with meals [6], reflecting the importance of gastric acidity in the process. Intestinal absorption of LT4 depends primarily on its dissolution in gastric acid secretion. Therefore, absorption may be affected by many causes altering gastric pH such as *Helicobacter pylori* infection and autoimmune gastritis [7, 8]. The mechanism by which intestinal absorption of LT4 may be impaired in patients with altered gastric pH is still unclear. However, it is possible that hydrophilic sodium salt (pharmaceutical LT4) remains undissociated in hypochlorydic gastric conditions and thus less absorbed [9, 10]. On the basis of this data, the majority of clinicians suggest that enteral feeding should be held 1–2 h prior to and after L-T4 administration despite lack of data with continuous enteral nutrition [11].

Traditionally, T4 is available in tablet form worldwide, but new formulations in soft gel capsule or liquid form are available now. As opposed to tablets, liquid L-T4 does not need to be dissolved before being absorbed, as has been shown recently by Yue et al. [12].

Recently, we showed that oral liquid L-T4 formulation could diminish the problem of L-T4 malabsorption caused by coffee when using traditional tablet formulations [13].

The aim of this study was to compare thyroid hormonal profile of patients submitted to L-T4 treatment in tablets or liquid formulation with an enteral feeding tube. The second objective was to assess the management of the two different formulations by nurses.

Patients and methods

From January 2011 to May 2013, we recruited 20 euthyroid patients submitted to total laryngectomy and thyroidectomy for laryngeal cancers. All the patients were consecutively randomized to start L-T4 treatment in tablet formulation (Group T) or liquid formulation (Group L) (Tirosint® fiala monouso, IBSA Farmaceutici Italia) the day after surgery with an enteral feeding tube and this was maintained for at least 21 days.

All the patients were fed with Nutrison® Standard formula (Nutricia Italia). Its characteristics are available at http://www.wolfdesign.it/pediatrianutrizionale/articoli/aziende/NUTRICIA/Nutrison%20Standard.pdf.

The replacement dose of L-T4 was 1.6 mcg per kg of body weight per day [9] for both tablet and liquid formulations.

Tablets were crushed before administration and enteral feeding was stopped for 30 min before and after L-T4 treatment to obtain an empty stomach; liquid formulation was placed immediately into the nasoenteric tube without the need for an empty stomach.

A thyroid hormonal profile was obtained for all the patients after 3 weeks of L-T4 replacement therapy.

All the patients received the same enteral nutrition with the same dosage.

A questionnaire about preparation and administration of L-T4 replacement therapy was given to the nurses, who had to choose from excellent [1], good [2] or poor [3], for both formulations.

Serum concentrations of free thyroxine (fT4; normal range 8.0–19.0 pg/mL, analytical sensitivity 1 pg/mL; intra- and inter-assay coefficient of variation, 2.4 and 6.8 %, respectively), free triiodothyronine (fT3; normal range 2.4–4.7 pg/mL; analytical sensitivity 0.35 pg/mL; intra- and inter-assay coefficient of variation, 4.6 and 6.5 %, respectively), and TSH (normal range 0.4–4.5 mIU/L, analytical sensitivity 0.004 mlU/L; intra- and inter-assay coefficient of variation, 2.5 and 5.7 %, respectively) were measured by means of immunochemoluminiscent assays using an automated analyser (Immulite 2000, DPC Cirrus, Los Angeles, CA, USA) employing commercial kits (Diagnostic Products Corporation, Los Angeles, CA, USA).

The protocol of the study was approved by the Ethics Committee of our institution (Medical School, University of Brescia). All the procedures were in accordance with our institutional guidelines and written informed consent was obtained from all subjects recruited in the study.

Statistical

Statistical analysis was performed using SPSS software (SPSS, Inc., Evanston, IL). Between the groups, comparisons of thyroid profile at baseline and after 3 weeks were performed by ANOVA.

Non-parametric variables were performed by χ^2 test. A p value <0.05 was considered statistically significant. Data were expressed as mean ± standard deviation.

Results

The clinical and biochemical features of the 20 euthyroid patients (Group T and Group L) at baseline (i.e., before laryngectomy and thyroidectomy), are summarized in Table 1. No difference in gender, age, BMI or thyroid hormonal profile between the two groups was observed.

Thyroid hormonal profile of all the patients before surgery and after 3 weeks of replacement L-T4 therapy is reported in Fig. 1. Specifically, no difference of TSH (2.79 ± 1.03 vs 2.81 ± 1.04 mUI/L), fT4 (12.68 ± 2.68

vs 12.62 ± 2.64 pg/mL) and fT3 levels (3.09 ± 0.62 vs 2.93 ± 0.43 pg/mL) before and after L-T4 treatment was observed among patients of Group L.

Also in Group T thyroid hormonal profile was super-imposable to pre-surgical data: in particular, no difference of TSH (2.50 ± 1.18 vs 2.94 ± 1.22 mUI/L, $p = 0.427$), fT4 (12.31 ± 1.89 vs 12.41 ± 1.62 pg/mL) and fT3 (3.21 ± 0.56 vs 3.03 ± 0.41 pg/mL) levels was found.

Preparation and administration of L-T4 liquid formulation were considered excellent by 12/13 nurses (92.3 %) whereas 10/13 (76.9 %) considered the tablet formulation to be poor. The result of the questionnaire is shown in Fig. 2.

Discussion

The main result of this study is that liquid L-T4 formulation can be administered immediately through the feeding tube. Second, nurses have clearly indicated the preference of liquid levothyroxine for managing patients in enteral nutrition therapy.

Maintaining appropriate nutrition in patients with acute and chronic diseases is an important part of standard medical and surgical care. Malnourished patients in comparison with well-nourished ones have poorer clinical results, more complications and infections, and use more health care resources [15–17]. If oral intake is inadequate or impossible, patients may receive enteral nutrition through a feeding tube [18]. Drug therapy might be complicated, since, for example, some medications may increase their bioavailability [19], or may obstruct the tube, therefore, for this reason use of liquid forms should be given preference whenever possible. Moreover, if the tube is placed in the stomach, the enteral feeding has to be interrupted for at least 30 min before and after administration of drugs requiring an empty stomach (i.e., levothyroxine) [18, 20].

Gastric acidity is in fact crucial for dissolution and absorption of many tablets. This is of particular relevance for patients in LT-4 replacement therapy, who are usually instructed to take the drug in the morning in a fasting state, prior to breakfast, to avoid possible interactions with food [2–6], dietary fibers [11, 13], coffee [14], coffee with milk [4], and other breakfast drinks altering gastric pH [15].

On the basis of this data, the majority of clinicians suggest that enteral feedings should be held 1–2 h prior and after L-T4 administration despite lack of data with continuous enteral nutrition [18], although 30 min have been proven sufficient [19].

Recently, Dickerson et al. [21], showed that more than half of the patients receiving concurrent L-T4 by enteral feeding developed subclinical or overt hypothyroidism within 2 or 3 weeks of therapy.

In our study, no patients (Group T and Group L) developed subclinical or overt hypothyroidism. Differently from Dickerson et al. [21], we must underline that enteral feedings of patients of Group T were given 30 min prior to and after L-T4 administration. On the contrary, subjects of Group L were administered liquid formulation concomitant with enteral nutrition.

Administering medication through enteral tubes is a key role of nurses in acute care settings [22]. In 1995, Seifert et al. [23] clearly showed that nurses prefer the use of

Table 1 Clinical and biochemical features of patients at baseline (i.e., before laryngectomy and thyroidectomy), in accordance with the different L-T4 formulations treatment after surgery

	Patients treated with L-T4 in tablet form	Patients treated with L-T4 in liquid form	*p* value
Patients (*n*)	10	10	–
Gender (M/F)	9/1	9/1	Ns
Age (years)	68 ± 5.8	69.1 ± 5.1	Ns
BMI (kg/cm^2)	23 ± 2.1	23.1 ± 1.9	Ns
TSH (mUI/L)	2.50 ± 1.18	2.79 ± 1.03	Ns
fT4 (pg/mL)	12.31 ± 1.89	12.68 ± 2.68	Ns
fT3 (pg/mL)	3.21 ± 0.56	3.09 ± 0.62	Ns

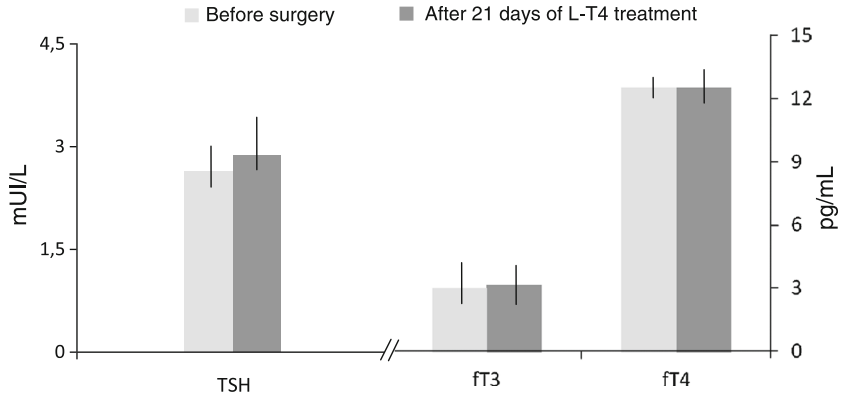

Fig. 1 Thyroid hormonal profile of all the patients before surgery and after L-T4 treatment

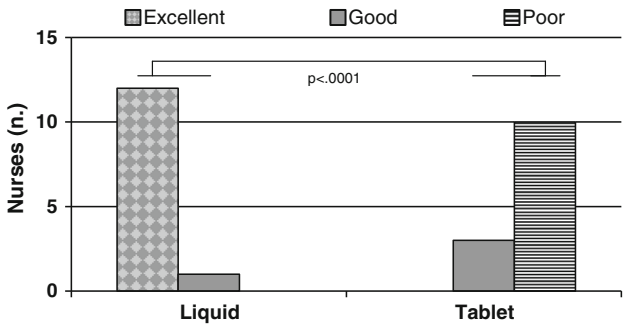

Fig. 2 Questionnaire results about therapy preparation and administration by nurses

liquid formulations than crushed tablets greatly reducing the time spent to prepare and administer therapy. In agreement with this view, our nurses (92.3 %) consider the management of liquid L-T4 formulation for patients with enteral feeding tube to be excellent.

Moreover, crushing tablets before administering them may present various problems, especially when crushing changes the medication pharmacokinetics and pharmacological properties [24]. Drugs formulated for oral administration undergo different processes of biotransformation: release, absorption, distribution, metabolism and excretion. When an individual changes the dosage form of certain oral solid medication, one of these processes may be altered [25]. For example, it has been shown that there is a significant difference in the mean concentration of L-T4 in patients treated by percutaneous endoscopic gastrotomy (PEG) due to the amount of medication lost during crushing and transfer, even if the Authors concluded that the amount of uptake of levothyroxine by PEG is probably clinically insignificant [26]. To the best of our knowledge, no data on the amount of the uptake of crushed L-T4 tablets by nasogastric tube are reported. Even if we admit a loss of amount of medication during crushing and transferring L-T4 tablets through a nasogastric tube, our data did not show any clinical relevance in agreement with Menessis et al. [26].

This study presents some limitations; first, the small number of patients enrolled in the study. To our knowledge, this is the first report focusing on this topic, and even if the results were obtained with a relatively small group of patients (20 subjects) they confirm the results previously obtained by our Group with a larger group of subjects [13]. This data reinforces our hypothesis that oral L-T4 liquid formulation could diminish the problem of L-T4 malabsorption caused by food when using traditional tablet formulations, as has also been recently confirmed both in adults and in children [27, 28].

Another issue could be represented by the possibility that food may reduce/change the stability of liquid levothyroxine. This important issue has been evaluated by a recent study by Bernareggi et al. [29] who demonstrated that liquid levothyroxine is stable in various hot beverages and in orange juice for at least 20 min.

Finally, there is the relatively short period of TSH re-evaluation (3 weeks). This might be of particular relevance in patients of Group T, since a non-significant increase of TSH was detected. As well known, TSH steady state is achieved about 4–8 weeks after the start of levothyroxine treatment; for this reason it is suggested that the serum TSH is evaluated no earlier than 4 weeks from initiating therapy or adjusting dosage of levothyroxine [30].

On the other hand, it has been demonstrated that 3 weeks of thyroxine withdrawal are enough to stimulate and increase endogenous TSH [31]. Moreover, in athyreotic patients serum-free T3 and mainly T4 depend only on levothyroxine therapy. Given that the thyroid hormonal profile (TSH, fT4 and fT3) did not change in our patients, even if in a short period of time, we believe that our data confirm our hypothesis and reinforces our results.

In conclusion, our data, even if obtained with a small number of subjects, have for the first time, clearly shown that liquid L-T4 formulation can be administered immediately through nasoenteric tube without the need for an empty stomach. Moreover, this formulation is more easily managed by nurses than with the tablet formulation in patients under enteral nutrition through a feeding tube.

Conflict of interest The authors declare no conflict of interest.

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