



Original Research

Role of pre-operative vitamin D supplementation to reduce post-thyroidectomy hypocalcemia; Cohort study



Mehreen Khan Bhattani^{a,*}, Mubarak Rehman^a, Moiz Ahmed^a, Humera Naz Altaf^b,
Usama Khalid Choudry^c, Kamran Hakeem Khan^a

^a Surgical Unit-II, Pakistan Institute of Medical Sciences, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad, Pakistan

^b Shifa College of Medicine, Shifa Tameer e' Millat University, Pakistan

^c Shifa International Hospital, Shifa Tameer e' Millat University, Pakistan

ARTICLE INFO

Keywords:

Thyroidectomy

Hypocalcemia

Vitamin D

Post-thyroidectomy complications

ABSTRACT

Introduction: Hypocalcaemia after thyroidectomy is observed with increasing frequency, often resulting in prolonged hospital stay with increased use of resources, delayed return to work and reduced quality of life. The administration of vitamin D is essential in the therapy of postoperative hypocalcaemia. What has not been examined so far is whether and how routine preoperative vitamin D prophylaxis can help to prevent postoperative hypocalcaemia.

Materials and methods: This is a prospective cohort study which was conducted from June 2016 to July 2017 at a tertiary care hospital. One hundred and two patients with thyroid disease who were admitted for thyroid surgery were interviewed and underwent physical examination and laboratory investigations. The patients enrolled in the study were randomly assigned to either the Interventional group (Pre-operative Vitamin D Supplementation) or the control group (placebo). The work is reported in line with the standards set by STROCCS criteria [1].

Results: Out of 102 patients there were 89 females (87.25%) and 13 males (12.7%) with a mean age of 39.35 ± 7.01 years. In the test group 45 (88.2%) patients had no clinical hypocalcemia, 5 (9.82%) had latent while 1 (2%) patient had overt hypocalcemic symptoms. In placebo group 37 (72.5%) had no clinical hypocalcemia, 10 (19.6%) had latent and 4 (7.8%) had overt hypocalcemic symptoms. (P-value < 0.05).

Conclusion: As the general population is deficient in Vitamin D, a prophylactic vitamin D dose given in immediate preoperative period can significantly reduce acute symptomatic postoperative hypocalcemia in patients undergoing thyroid surgery.

1. Introduction

Thyroidectomy is one of the most common interventions in general and endocrine surgery with a wide range of indications including but not limited to compression induced symptoms, malignancy or suspected malignancy, hyperthyroidism, and cosmesis [1,2]. Post-operative hypocalcaemia is a recognized complication of thyroid surgery. Although most of the patients recover, yet permanent hypoparathyroidism ranges from 1 to 32% of patients undergoing thyroid surgery. Parathyroid gland injury can result from inadvertent removal, interruption of blood supply and haematoma formation [3]. In fact, the most common cause of acute symptomatic hypocalcemia in hospitalized patients is parathyroid gland disruption following total thyroidectomy [4,5]. (see Tables 4–7)

Much literature focuses on post-thyroidectomy hypocalcemia [6,7], however the reported incidence of this complication varies greatly from 0.3 to 49% for transient hypocalcemia and 0–13% for permanent hypocalcemia [8]. Transient hypocalcemia is defined as a state when exogenous calcium supplements are required either to maintain normal serum calcium levels or to correct the clinical signs and symptoms of hypocalcemia [6]. Permanent hypocalcemia is labelled when the patient requires calcium and vitamin D supplements for more than 6 months [6]. The discrepancy in the incidence of post-operative hypocalcemia in past literature could be attributed to the fact that various operational definitions have been used to define hypocalcemia in different studies, with some authors documenting hypocalcemia if the patient shows evidence of clinical signs and symptoms, whereas others considered hypocalcemia if the serum calcium levels fell below a

* Corresponding author. House no.418, street 27, Sector E-11/4, Islamabad, 44000, Pakistan.

E-mail addresses: mehreenkhan.b@gmail.com (M. Khan Bhattani), khyberkhanjungi@gmail.com (M. Rehman), Moiz1491@gmail.com (M. Ahmed), humeraaltaaf@gmail.com (H.N. Altaf), uk_choudry@hotmail.com (U.K. Choudry), kamranhakeemkhan@gmail.com (K.H. Khan).

<https://doi.org/10.1016/j.ijisu.2019.08.035>

Received 19 June 2019; Received in revised form 8 August 2019; Accepted 28 August 2019

Available online 05 September 2019

1743-9191/ © 2019 IJS Publishing Group Ltd. Published by Elsevier Ltd. All rights reserved.

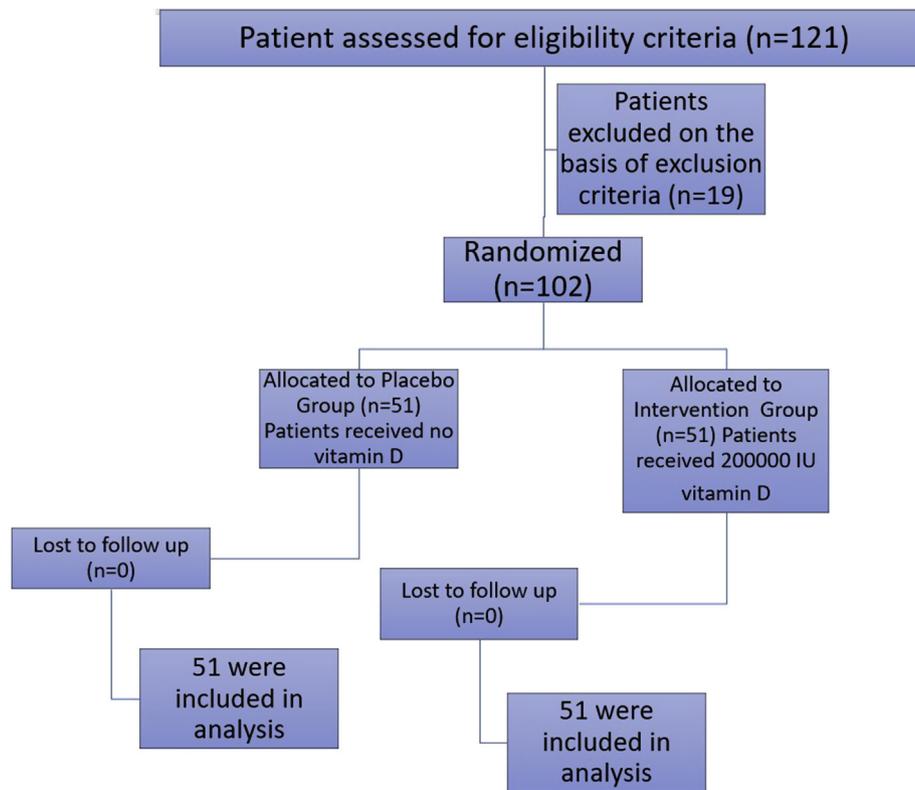


Fig. 1. Patients distribution organogram.

certain threshold [9,10]. Literature search also suggests that another reason could be the fact that various studies have assessed post-operative hypocalcemia after different thyroid surgical procedures, with some literature also including procedures like thyroid lobectomy in their sample which would underestimate the incidence of hypocalcemia leading to misinterpretation [11].

Hypocalcemia following thyroid surgery is caused either due to parathyroid devascularization, stunning, or accidental removal of the parathyroid glands [12]. Multiple risk factors have been identified which predispose patients to develop post-operative hypocalcemia.

In light of the available evidence of prevalent vitamin D deficiency in the general population, and the observation of appearance of post-thyroidectomy hypocalcemic symptoms at a much earlier stage than documented in previous literature, we postulate that a prophylactic vitamin D supplementation dose given in immediate preoperative period can significantly reduce acute symptomatic postoperative hypocalcemia in patients undergoing thyroid surgery (see Fig. 1).

2. Methods

The study was at tertiary care hospital after approval from institution's Ethical Committee. The duration of study was one year, from June 2016 to July 2017. The work has been reported in line with the STROCSS criteria [1].

All the patients undergoing total thyroid surgery during the study period were included in the study. Exclusion criteria included decreased preoperative corrected serum calcium levels (less than or equal to 8.0 mg/dL or 2.0 mEq/dL), renal insufficiency (serum creatinine levels less than or equal to), or if the subjects had any condition affecting the serum vitamin D levels (other than decreased exposure to light or malnutrition) such as celiac disease or any small intestinal disorder affecting the absorption of Vitamin D and calcium, or drugs (including antiepileptic drugs, bisphosphonates, cisplatin, aminoglycosides, diuretics, or proton pump inhibitors). A total of 102 subjects were

enrolled in the study and were randomly assigned to either the test group or the control group. An informed consent was obtained from all the participants at the time of enrollment into the study.

All participants undergoing thyroid surgery were admitted 1 day before the surgery and their demographic data was recorded. In addition to the preoperative workup, the laboratory values recorded included complete blood picture, serum calcium levels, serum albumin levels, and serum creatinine levels. Corrected serum calcium level was then calculated using the formula: serum calcium + 0.8x (4 - serum albumin).

Patients were then randomly assigned to either the test or the control group. Subjects in the test group were subjected to the intervention while the patients in the control group received the placebo, but neither the researcher nor the nurses knew which medications were being given.

In the test group, patients received one dose of Vitamin D 200000 IU PO at the time of admission, along with 700 mg of calcium carbonate per day PO in two divided doses for 2 days preoperatively. The control group received only 700 mg of calcium carbonate per day PO in two divided doses for 2 days preoperatively, but no Vitamin D.

Following thyroid surgery, each patient was kept under observation for at least 24-h and was discharged only if they displayed no signs and symptoms of hypocalcemia, hemorrhage, hoarseness of voice, or any other post-operative complications. The investigations done post-operatively included serum calcium and serum albumin levels. Clinical outcomes that were observed were divided into three categories, i.e. clinically evident or symptomatic hypocalcemia, latent hypocalcemia, and biochemical hypocalcemia. Clinically evident hypocalcemia was defined if the patients experienced any of the hypocalcemic symptoms including, but not limited to, perioral or digital paresthesias, tetany or carpopedal spasms, laryngospasms, EKG changes (prolonged QT interval) or arrhythmias, or seizures. In the absence of hypocalcemic symptoms, patients were regularly checked for the presence of Chvostek's sign and Trousseau's sign every 3 h, which if elicited would

categorize the subject into the latent hypocalcemia group. The last category was biochemical hypocalcemia which included subjects who showed no signs and symptoms of hypocalcemia but still had a low corrected serum calcium levels (less than or equal to 8 mg/dL or 2 mEq/dL).

If none of the outcomes were observed in the patients, they were discharged after 24-h, with the instructions that if any of the symptoms of hypocalcemia appear they should report back to the hospital immediately, or if not then they should follow up in 2 weeks and 4 weeks at which time the laboratory investigations were repeated to look for any biochemical hypocalcemia. The discharge medications included Vitamin D PO 800 IU per day for 1 month, along with calcium carbonate 1000 mg/day in 3 divided doses for 1 month.

2.1. Statistical analysis

Data was recorded and analyzed using Statistical Package for Social Sciences v22.0 (SPSS). Descriptive statistics were calculated for both qualitative and quantitative variables. Mean ± SD was calculated for demographic data. Qualitative variables were presented through tables and figures. P value was calculated by chi square and value of < 0.05 was considered statistically significant.

3. Results

Mean age of the study population was 39.35 ± 7.01 years with a minimum age of 22 years and maximum of 54 years. Amongst the test group 45 (82.2%) were female and 6 (11.8%) were male. In placebo group we had 44 (86.3%) females and 7 (13.7%) males.

In the test group 36 (70.6%) had multinodular goiter, 5 (9.8%) patients were suffering from carcinoma thyroid and 10 (19.6%) had thyroiditis. Meanwhile in placebo group, 36 (70.6%) had multinodular goiter, 3 (5.9%) patients were suffering from carcinoma thyroid and 12 (23.2%) had thyroiditis.

In the test group 32 (62.7%) patients underwent total thyroidectomy, 16 (31.4%) underwent near total thyroidectomy and 3 (5.9%) underwent subtotal thyroidectomy. While in placebo group, 36 (70.6%) patients underwent total thyroidectomy, 14 (27.5%) underwent near total thyroidectomy and 1 (2.0%) underwent subtotal thyroidectomy.

On the first post-operative day, 7 (13.7%) had hypocalcemia biochemically whereas 44 (86.3%) had normal serum calcium levels in test group. However, in placebo group, 12 (23.5%) had hypocalcemia biochemically while 39 (76.5%) had normal serum calcium levels.

On the third post-operative, 1 (2.9%) had hypocalcemia biochemically whereas 50 (98.0%) had normal serum calcium levels in test group. However, in placebo group, 4 (7.8%) had hypocalcemia biochemically while 47 (92.2%) had normal serum calcium levels.

Out of 102 patients, 17 (18.6%) had hypocalcemia, biochemically on 1st post-operative day and 04 (3.9%) had on 3rd post-operative day. In the test group, 45 (88.2%) did not show any clinical symptoms of hypocalcemia, However, In placebo group, 36 (72.0%) did not show any clinical symptoms of hypocalcaemia. On independent samples analysis, there was a statistically significant difference in the mean calcium levels between the interventional group and control group on day 1, day 7 and day 30 (Table 1. P < 0.05). The risk of developing postoperative hypocalcaemia was 3.1 times higher in placebo group compared to study group (Table 2 P < 0.048) (see Table 3).

Table 1 Age of patients.

Group	Minimum Age (years)	Maximum Age (years)	Mean Age (years)	Std. Deviation
Vitamin D Supplement	22years	54	38.88	7.50
Placebo Group	23	50	39.82	6.52

Table 2 Gender of patients.

Group		Frequency	Percent
Vitamin D supplement	male	6	11.8
	female	45	88.2
	Total	51	100.0
placebo	male	7	13.7
	female	44	86.3
	Total	51	100.0

Table 3 Reason for thyroidectomy.

Group	Disease	Frequency	Percentage
Vitamin D Supplement	Toxic MNG	13	25.4
	Pressure Symptoms	19	37.2
	Cosmetic	4	7.8
	Carcinoma	5	9.8
	Thyroiditis	10	19.6
	Total	51	100.0
Placebo	Toxic MNG	14	27.4
	Pressure Symptoms	17	33.3
	Cosmetic	5	9.8
	Carcinoma	3	5.9
	Thyroiditis	12	23.5
	Total	51	100.0

Table 4 Procedure performed.

Group	Procedure	Frequency	Percent
vitamin D supplement	total thyroidectomy	32	62.7
	near total	16	31.4
	Subtotal	3	5.9
	Total	51	100.0
Placebo	total thyroidectomy	36	70.6
	near total	14	27.5
	Subtotal	1	2.0
	Total	51	100.0

Table 5 Clinical evidence of hypocalcemia.

Group	Clinical Hypocalcemia	Frequency	Percent
Vitamin D supplement	none	45	88.2
	latent	5	9.8
	overt	1	2.0
	Total	51	100.0
Placebo	none	37	72.5
	latent	10	19.6
	overt	4	7.8
	Total	51	100.0

4. Discussion

Among the surgical procedures, total thyroidectomy [13,14], repeat thyroidectomy [13], and thyroidectomy along with neck dissection [13] increases the risk for the development of this complication. Thyroidectomy done for certain pathologies like advanced thyroid cancer [13–17], Grave's disease [18] and Hashimoto's thyroiditis [19],

Table 6

Independent samples *t*-test showing statistically significant difference in post-operative calcium levels between experimental arm and control arm.

	Groups	Mean	t	2-tail sig	95% Confidence Interval	
					Lower	Upper
Pre op CA	Drug	9.67	0.452	0.65	0.11	0.19
	Placebo	9.63				
Day 1	Drug	9.70	5.72	< 0.01	0.59	1.22
	Placebo	8.79				
Day 7	Drug	9.80	6.14	< 0.05	0.47	0.93
	Placebo	9.09				
Day 30	Drug	9.91	6.09	< 0.05	0.36	0.72
	Placebo	9.37				

Table 7

Comparison of hypocalcemia in interventional and placebo group.

	PLACEBO	DRUG	P value
Hypocalcemia	15 (29.4%)	6 (11.7%)	< 0.05
Normocalcemia	31 (60.8%)	45 (88.2%)	

hyperthyroidism [14,17], large volume goiter [14] with retrosternal extension [14,16], and recurrent goiters [14,15] have also been shown to predispose patients to post-operative hypocalcemia [13–20].

In his study SS Abadin has reported data of medical malpractice suits for thyroid surgery from over 20 years. He found 143 medical malpractice suits following thyroid surgery. Injury to recurrent laryngeal nerve was identified as the cause for law suit in about 10% of cases, with a bilateral damage in about 3%. Italy has seen a steep rise in malpractice cases in thyroid surgery. A database research performed on the two certified Italian lawsuit search engine “De Jure” and “Le leggi d’Italia”, showed 23 cases of medical lawsuits over 10 years i-e from 2004 to 2014. Patients won the lawsuits in majority of cases affecting heavy penalties to surgeons as compensation for patients. Surgeons inability to adequately complete surgical procedure notes and demonstrate their scrupulous surgical technique, meet the requirements of informed consent and a late interaction with patient in postoperative period to communicate about occurrence of nerve injury have been frequently found to be responsible for losses in these lawsuits [14].

A large series has demonstrated that almost 70% of patients with anaplastic carcinoma show invasion of surrounding structures: muscles (65%), trachea (46%), oesophagus (44%), laryngeal nerve (27%), and larynx (13%), at the time of initial clinical presentation [15]. Death usually occurs from direct invasion and obstruction of trachea and oesophagus, as well as distant metastatic involvement. Surgery in form of total thyroidectomy or a debulking procedure remains the mainstay of treatment for anaplastic carcinoma to improve at least compressive complications [16].

Hypocalcemia following thyroid surgery is caused either due to parathyroid devascularization, stunning, or accidental removal of the parathyroid glands [12]. Multiple risk factors have been identified which predispose patients to develop post-operative hypocalcemia. Among the surgical procedures, total thyroidectomy [13,14], repeat thyroidectomy [13], and thyroidectomy along with neck dissection [13] increases the risk for the development of this complication. Thyroidectomy done for certain pathologies like advanced thyroid cancer [13–18], Grave’s disease [18] and Hashimoto’s thyroiditis [19,20], hyperthyroidism [14], large volume goiter [14] with retrosternal extension [14–16], and recurrent goiters [14,15,17] have also been shown to predispose patients to post-operative hypocalcemia. Another factor noted by Ahmad et al. is malnutrition of the patients which results in decreased preoperative total body calcium, proteins, and vitamin D levels [21].

Hypocalcemia varies from an asymptomatic biochemical

abnormality to a life threatening disorder, depending on several factors such as duration, severity and rapidity of the fall of calcium levels [22]. In severe forms of acute hypocalcemia (with an ionized calcium level less than 1.1 mmol/L), tetany and seizures are frequently observed [22]. However, in milder forms symptoms like paresthesias and numbness of the fingertips and perioral area have been reported [22]. Among the clinical signs observed, Chvostek and Trousseau signs are the ones most commonly elicited, with Trousseau sign being more specific for hypocalcemia [23]. Prolonged contraction of the laryngeal and respiratory muscles may lead to stridor and cyanosis [22].

Literature has not kept much focus on the time lapse between thyroid surgery and the development of hypocalcemia. A study carried out in Iran found that the average time for the development of clinical symptoms of hypocalcemia was 41.25 ± 11.5 h, with symptoms occurring significantly earlier in females (36.5 ± 9.6 h) as compared to males (51.5 ± 8.5 h; $p = 0.001$) [24]. However, some studies have also reported hypocalcemic signs appearing in patients much earlier. Nair et al. conducted a study in India and reported that 11.05% of the subjects developed hypocalcemia within 6 h after surgery [7]. Similarly, Ahmad et al. showed that 9.3% of the patients developed hypocalcemia within the first 24 h following thyroidectomy [21]. The authors also observed in an unpublished data that most of the patients undergoing thyroid surgery in a major government hospital in Islamabad, Pakistan developed hypocalcemia within 24 h.

The earlier appearance of hypocalcemic symptoms in these patients have been attributed to diminished preoperative total body calcium levels, prevalent in the general population, as reasoned by Ahmad et al. [21]. The most common cause of decreased calcium levels in primary care is hypovitaminosis D, and depending on the demographics it may be as prevalent as 50% [24–26]. Vitamin D deficiency has emerged as a pandemic [27–31], with particular strongholds in the developing countries.

In the past, much research has focused on ways to reduce hypocalcemia following thyroid surgery. The proposed methods can be broadly divided into either targeted intervention of high risk individuals or widespread intervention. Targeted intervention includes techniques identifying high risk individuals such as monitoring serum PTH levels either intraoperatively or postoperatively, or serial post-operative serum calcium [17,18]. However, these tests are costly and are not always available in most hospitals in the developing countries, making it an impractical option in these countries.

Another way proposed is by auto-transplantation of parathyroid glands in either the sternocleidomastoid muscle, if they are either removed accidentally or have sustained a vascular injury [3]. This method has shown great potential in prevention of permanent hypocalcemia, however transient hypocalcemia was commonly seen in the subjects for which the mean time for correction was two weeks [3].

In widespread intervention, all patients were given either oral calcium or calcium along with Vitamin D in the postoperative period regardless of their risk of development of the complication [19,20]. Even though this intervention decreases the incidence of post-operative hypocalcemia, the risk is not completely eradicated. In fact some subjects even on the intervention developed symptomatic hypocalcemia significant enough to warrant IV calcium gluconate [21].

The results of this study have shown that in a population with known widespread Vitamin D deficiency [13,22], patients undergoing any form of thyroid surgery are at an increased risk of developing post-operative hypocalcemia within the first 24 h, even though the pre-operative serum calcium levels are within the normal range. This is in congruence with the results found by Nair et al. and Ahmad et al. that post-operative hypocalcemia presents much earlier than proposed in earlier studies, most probably due to the widespread Vitamin D deficiency [8,9].

Anne K et al. in their trial concluded comparable results to our study. In their study cohort, preoperative calcium and vitamin D administration had significant benefit in the patient overall outcome.

Patients of the intervention group had elevated calcium levels in the postoperative period, low requirement for intravenous calcium administration, less number of symptomatic hypocalcaemia patients and reduced length of hospital stay. However, in stark contrast to ours, their study included 85% of thyroid carcinoma patients, who may have elevated risk of developing postoperative hypocalcemia and hence may have greater advantage from the respective preoperative supplemental treatment [23].

Sumiya Jaan and et al. in their randomized trial administered calcium and vitamin D seven days preoperatively and continued the supplementation in the postoperative period. Their results demonstrated significantly reduced postoperative hypocalcemia. As well as this, need for intravenous management of severe symptomatic hypocalcemia was completely eliminated in the interventional group [24].

Furthermore, the protocol implemented in this study showed that if patients are given a load of Vitamin D along with Calcium before undergoing thyroid surgery, then the incidence of hypocalcemia is significantly reduced, and that post-operative interventions alone are not enough.

Among healthy adults living in an urban area in Tehran, Iran, Hashemipour et al. estimated that vitamin D deficiency amounted to 79.6% [32]. Similarly in India different studies showed that vitamin D deficiency occurred in 80–85% of the population [33].

In Pakistan multiple studies have documented low vitamin D levels in the healthy population. A cross-sectional study done on healthy employees of a tertiary care hospital in Karachi revealed 90% of the subjects having hypovitaminosis D [34]. Another research in similar settings showed a prevalence of 92% of vitamin D deficiency [35]. Masood et al. also estimated that 77.5% of the subjects are deficient in vitamin D [36].

Limitations of this study include that the subjects in both groups were not crossed over, due to time and resource constraint. Crossing over between the test and the control groups would have provided further validity to the results of the study. Also, subjects were only followed up to 1 month during which development of transient hypocalcemia was observed. However, the effect of the intervention could not be studied on the development of permanent hypocalcemia. Therefore, further studies are needed testing this protocol on a larger sample size, with a longer follow up to further elucidate the effect of preoperative Vitamin D load on the development of post-thyroidectomy hypocalcemia.

5. Conclusion

Hypocalcemia is one of the major causes of morbidity in patients after thyroid surgery. Multiple causative factors have been described which predispose patients to develop this complication. As the general population is deficient in Vitamin D, a prophylactic vitamin D supplementation dose given in immediate preoperative period can significantly reduce acute symptomatic postoperative hypocalcemia in patients undergoing thyroid surgery.

Data statement

Due to institutional policy regarding patient data confidentiality, we are unable to share the raw data of our research study.

Ethical approval

ERC approval was done.

Sources of funding

Self financed.

Conflicts of interest

Nil.

Trial registry number

Chinese Clinical Trials Registry.
ChiCTR1900023845.
<http://www.chictr.org.cn>.

Guarantor

Dr Mubarik Rehman Senior Registrar Shifa Tameer e millat university.

Provenance and peer review

Not commissioned, externally peer-reviewed.

CRediT authorship contribution statement

Mehreen Khan Bhattani: Data curation, Formal analysis, Writing - original draft. **Mubarik Rehman:** Conceptualization, Data curation, Formal analysis, Writing - original draft. **Moiz Ahmed:** Data curation, Formal analysis. **Humera Naz Altaf:** Writing - original draft. **Usama Khalid Choudry:** Writing - original draft. **Kamran Hakeem Khan:** Data curation, Formal analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijssu.2019.08.035>.

References

- [1] R.A. Agha, M.R. Borrelli, M. Vella-Baldacchino, R. Thavayogan, D.P. Orgill, for the STROCSS Group, The STROCSS statement: strengthening the reporting of cohort studies in surgery, *Int. J. Surg.* 46 (2017) 198–202.
- [2] M. Sokouti, V. Montazeri, S. Golzari, The incidence of transient and permanent hypocalcemia after total thyroidectomy for thyroid cancer, *Int. J. Endocrinol. Metab.* 1 (2010) 7–12.
- [3] N. Ahmed, M. Aurangzeb, M. Muslim, M. Zarin, Routine parathyroid auto-transplantation during total thyroidectomy: a procedure with predictable outcome, *JPMMA* 63 (2013) 190–193.
- [4] P.V. Pradeep, A. Agarwal, M. Baxi, G. Agarwal, S.K. Gupta, S.K. Mishra, Safety and efficacy of surgical management of hyperthyroidism: 15-Year experience from a tertiary care center in a developing country, *World J. Surg.* 31 (2) (2007) 306–312.
- [5] R.L. Baldassarre, D.C. Chang, K.T. Brumund, M. Bouvet, Predictors of hypocalcemia after thyroidectomy: results from the nationwide inpatient sample, *ISRN Surg.* 2012 (2012) 838614, <https://doi.org/10.5402/2012/838614>.
- [6] O. Thomusch, A. Machens, C. Sekulla, et al., Multivariate analysis of risk factors for postoperative complications in benign goiter surgery: prospective multicenter study in Germany, *World J. Surg.* 24 (11) (2000) 1335–1341.
- [7] V. Walker Harris, S. Jan De Beur, Postoperative hypoparathyroidism: medical and surgical therapeutic options, *Thyroid* 19 (2009), <https://doi.org/10.1089/thy.2008.0306.967-793>.
- [8] C.G. Nair, M.J.C. Babu, R. Menon, P. Jacob, Hypocalcemia following total thyroidectomy: an analysis of 806 patients, *Indian J. Endocrinol. Metabol.* 17 (2) (2013) 298–303.
- [9] A. Ahmad, H.M. Khan, N. Chaudhry, A.U. Qureshi, T.A. Shah, Post-thyroidectomy hypocalcemia—an audit of 100 cases, *Annals* 12 (2) (2006) 285–287.
- [10] R. Garg, N. Garg, N. Tandon, M.L. Khurana, A.C. Ammini, Idiopathic hypoparathyroidism presenting as epilepsy in a 40 years female, *Neurol. India* 47 (1999) 244–245.
- [11] M. Hosseini, H.A. Ottaghvar, A. Tizmaghz, G. Shabestanipour, P.A. Vahid, Evaluating the time interval for presenting the signs of hypocalcemia after thyroidectomy, *J. Clin. Diagn. Res.* 10 (3) (2016) 19–22, <https://doi.org/10.7860/JCDR/2016/15274.7445> PubMed Central PMCID: PMC4843313.
- [12] L.M. Zuberi, A. Habib, N. Haque, A. Jabbar, Vitamin D Deficiency in ambulatory patients, *J. Pak. Med. Assoc.* 58 (2008) 482–484.
- [13] Z. Masood, Q. Mahmood, K.T. Ashraf, Vitamin D deficiency—an emerging public health problem in Pakistan, *JUMDC* 1 (1) (2010) 4–9.
- [14] C. Gambardella, A. Polistena, A. Sanguinetti, R. Patrone, S. Napolitano, D. Esposito, et al., Unintentional recurrent laryngeal nerve injuries following thyroidectomy: is it the surgeon who pays the bill? *Int. J. Surg.* 41 (2017) 55–59, <https://doi.org/10.1016/j.ijssu.2017.08.035>.

- 1016/j.ijsu.2017.01.112.
- [15] O. Derbel, S. Limem, C.S. Ferlay, J.C. Lifante, C. Carrie, J.L. Peix, et al., Results of combined treatment of anaplastic thyroid carcinoma (ATC), *BMC Canc.* 469 (2011) 1–8 <http://www.biomedcentral.com/1471-2407/11/469>.
- [16] G. Conzo, A. Polistena, P.G. Calò, P. Bononi, C. Gambardella, C. Mauriello, et al., Efficacy of combined treatment for anaplastic thyroid carcinoma: results of a multinstitutional retrospective analysis, *Int. J. Surg.* 12 (2014) 178–182 <https://doi.org/10.1016/j.ijsu.2014.05.015>.
- [17] J.H. Kim, M.K. Chung, Y.I. Son, Reliable early prediction for different types of post-thyroidectomy hypocalcemia, *Clin. Exp. Otorhinolaryngol.* 4 (2) (2011) 95–100.
- [18] T.N. Le, P.D. Kerr, D.E. Sutherland, P. Lambert, Validation of 1-hour post-thyroidectomy parathyroid hormone level in predicting hypocalcemia [published correction appears in *J Otolaryngol Head Neck Surg*, *J. Otolaryngol. Head Neck Surg.* 43 (2014) 42, <https://doi.org/10.1186/1916-0216-43-5> 2014; 43(1):5. Published 2014 Jan 29.
- [19] J.L. Roh, C.I. Park, Routine oral calcium and vitamin D supplements for prevention of hypocalcemia after total thyroidectomy, *Am. J. Surg.* 192 (5) (2006) 675–678.
- [20] A. Alhefdhi, H. Mazeh, H. Chen, Role of postoperative vitamin D and/or calcium routine supplementation in preventing hypocalcemia after thyroidectomy: a systematic review and meta-analysis, *The Oncologist* 18 (5) (2013) 533–542.
- [21] D. Pisaniello, D. Parmeggiani, A. Piatto, N. Avenia, M. d'Ajello, M. Monacelli, F. Calzolari, A. Sanquinetti, U. Parmeggiani, P. Sperlongano, Which therapy to prevent post-thyroidectomy hypocalcemia? *Geka Chiryo* 26 (10) (2005) 357–361.
- [22] M.Z. Majeed, M. Saeed, A. Manzur, Frequency and risk factors for serum vitamin D deficiency among females of Pakistan, *JSZMC* 5 (2) (2014) 622–626.
- [23] M.L. Shih, J.A. Lee, C.B. Hsieh, J.C. Yu, H.D. Liu, E. Kebebew, et al., Thyroidectomy for Hashimoto's thyroiditis: complications and associated cancers, *Thyroid* 18 (2008) 729–734.
- [24] A. Ahmad, H.M. Khan, N. Chaudhry, A.U. Qureshi, T.A. Shah, Post-thyroidectomy hypocalcemia-an audit of 100 cases, *Annals* 12 (2) (2006) 285–287.
- [25] J. Turner, G. P. Selby, Society for Endocrinology Clinical Committee, Society for endocrinology endocrine emergency guidance: emergency management of acute hypocalcaemia in adult patients, *Endocr. Connect.* 5 (5) (2016) 7–8, <https://doi.org/10.1530/EC-16-0056>.
- [26] F.L. Urbano, Signs of hypocalcemia: Chvostek's and Trousseau's, *Hosp. Physician* 36 (2000) 43–45.
- [27] M. Hosseini, H.A. Otaghvar, A. Tizmaghz, G. Shabestanipour, P.A. Vahid, Evaluating the time interval for presenting the signs of hypocalcemia after thyroidectomy, *J. Clin. Diagn. Res.* 10 (3) (2016) 19–22, <https://doi.org/10.7860/JCDR/2016/15274.7445> PubMed Central PMCID: PMC4843313.
- [28] M.F. Holick, Vitamin D deficiency, *N. Engl. J. Med.* 357 (2007) 266–281.
- [29] M.F. Holick, High prevalence of vitamin D inadequacy and implications for health, *Mayo Clin. Proc.* 81 (3) (2006) 353–373.
- [30] A.H. Khan, R. Iqbal, Vitamin D deficiency in an ample sunlight country, *J. Coll. Phys. Surg. Pak.* 19 (5) (2009) 267–268.
- [31] P. Lips, Worldwide status of vitamin D nutrition, *J. Steroid Biochem. Mol. Biol.* 121 (2010) 297–300.
- [32] S. Hashemipour, B. Larijani, H. Adibi, M. Sedaghat, M. Pajouhi, et al., The status of biochemical parameters in varying degrees of vitamin D deficiency, *J. Bone Miner. Metab.* 24 (2006) 213–218.
- [33] C.V. Harinarayan, Prevalence of vitamin D insufficiency in postmenopausal south Indian women, *Osteoporos. Int.* 16 (2005) 397–402.
- [34] S. Mansoor, A. Habib, F. Ghani, Z. Fatmi, S. Badruddin, et al., Prevalence and significance of vitamin D deficiency and insufficiency among apparently healthy adults, *Clin. Biochem.* 43 (2010) 1431–1435.
- [35] L.M. Zuberi, A. Habib, N. Haque, A. Jabbar, Vitamin D Deficiency in ambulatory patients, *J. Pak. Med. Assoc.* 58 (2008) 482–484.
- [36] Z. Masood, Q. Mahmood, K.T. Ashraf, Vitamin D deficiency-an emerging public health problem in Pakistan, *JUMDC* 1 (1) (2010) 4–9.