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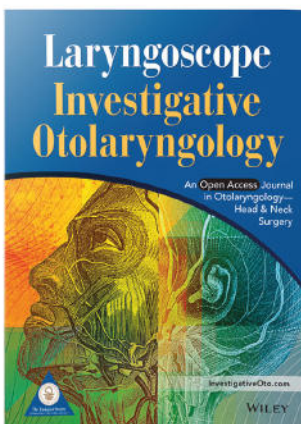


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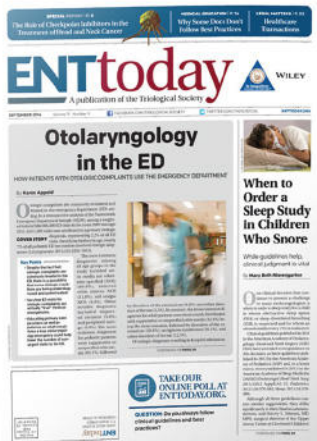


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ORIGINAL RESEARCH

Hypocalcaemia in pharyngolaryngectomy: Preservation or autotransplantation of parathyroid glands

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Abstract

Objective: To describe transient and permanent hypocalcaemia following partial and total pharyngolaryngectomy with parathyroid gland preservation or autotransplantation.

Methods: Thirty patients underwent partial or total pharyngolaryngectomy by a single surgeon during the period 2009-2020. Intraoperative parathyroid gland preservation or autotransplantation (where the gland appeared devascularized) was routinely performed. Calcium levels performed on day 1, 3 months, and at 12 months postoperatively were collected. Rates of transient and permanent hypocalcaemia were calculated.

Results: A total of 13% of patients had transient hypocalcaemia, and 10% permanent hypocalcaemia. Rates of transient and permanent hypocalcaemia in total pharyngolaryngectomy were 14% and 14%, respectively. Partial pharyngectomy hypocalcaemia rates were 13% for transient and 0% for permanent. The majority of patients underwent salvage surgery for oncological resection, often following radiotherapy (63%). Ipsilateral hemithyroidectomy was preferred to total (57% vs 7%), with high rates of concurrent neck dissection (67%) and reconstruction (87%).

Conclusion: This data supports preservation or autotransplantation of parathyroid glands as a means of reducing permanent postoperative hypocalcaemia.

Level of Evidence: Level IV, case series, retrospective.

KEYWORDS

hypocalcaemia, pharyngolaryngectomy, salvage surgery

1 | INTRODUCTION

Hypocalcaemia is common following total pharyngolaryngectomy, occurring in up to 65% of patients.¹ There is limited literature describing hypocalcaemia rates following pharyngolaryngectomy with

parathyroid preservation or autotransplantation. NCCN guidelines recommend central neck dissection and ipsilateral or bilateral neck dissection, and ipsilateral hemithyroidectomy, or total thyroidectomy for advanced hypopharyngeal cancer.² Unintentional devascularization of the parathyroid glands often occurs as a result of

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central neck dissection or mobilization of the larynx.³ Preservation or autotransplantation (where the gland appears devascularized) of the parathyroid gland may reduce risk of postoperative hypocalcaemia in these patients.

Previous authors have identified various risk factors for postoperative transient and permanent hypocalcaemia, including; total thyroidectomy,⁴ salvage laryngectomy, total pharyngectomy,⁵ and bilateral neck dissection.^{5,6} Often patients undergoing laryngectomy and pharyngolaryngectomy are paired together in retrospective analysis.

The aim of this study was to describe transient and permanent hypocalcaemia rates in patients undergoing total or partial pharyngolaryngectomy with preservation or autotransplantation of the parathyroid gland.

2 | MATERIALS AND METHODS

2.1 | Study population

All patients undergoing total or partial pharyngolaryngectomy were considered for inclusion in this study. Thirty patients were retrospectively identified between December 2009 and September 2020. Procedures were performed by a single surgeon (SJP, senior author) at the Department of Otolaryngology Head and Neck Surgery at The Wollongong Hospital, Wollongong, Australia.

2.2 | Surgical details

Central and ipsilateral neck dissection was routinely performed. Ipsilateral thyroidectomy was performed in those with unilateral disease and total thyroidectomy in those with bilateral laryngeal involvement. Decision to perform thyroidectomy was based upon suspicion of extra laryngeal disease extension (eg, radiological evidence of thyroid cartilage invasion or cricoarytenoid joint invasion). Parathyroid glands were routinely identified, and the gland preserved if blood supply was deemed intact intra-operatively. Autotransplantation of the parathyroid gland was performed if it appeared devascularized or was inadvertently removed during dissection. Excised parathyroid tissue was finely sliced, suspended in isotonic saline, with injection into the ipsilateral sternocleidomastoid muscle, as per Gauger et al.⁷

2.3 | Postoperative calcium monitoring and supplementation

In the immediate postoperative period, calcium levels were taken on day 1 and then as clinically indicated to guide replacement.

Calcium supplementation was guided by a predefined departmental protocol, included below:

1. Corrected calcium level 2.0-2.09 mmol/L:
 - a. Check twice daily, if trending down then proceed to step 2.
 - b. If trending up, continue twice daily monitoring until two consecutive levels ≥ 2.1 mmol/L.
2. Corrected calcium level 1.8-1.99 mmol/L OR trending down (as above):
 - a. Asymptomatic: Commence oral calcium and vitamin D supplementation
 - b. Symptomatic or signs of hypocalcaemia: Commence parenteral supplementation with calcium gluconate
3. Corrected calcium level < 1.8 mmol/L: Commence parenteral supplementation

Further corrected calcium levels were taken at 3- and 12-months following surgery in all patients. Approval for this study was obtained from the human research ethics committee attached to our local health district.

2.4 | Data collection

Demographic and clinical data included age, pathological diagnosis and stage, procedure performed, total or hemithyroidectomy, salvage or primary procedure (surgical, chemotherapy or radiotherapy), concurrent neck dissection, reconstruction method, discharge date, and other relevant endocrinological serum studies during admission (such as levels of parathyroid hormone, thyroid stimulating hormone, thyroxine, triiodothyronine, and vitamin D). TNM staging data are reported as recurrent TNM staging in salvage, and primary TNM staging in primary cases (AJCC Staging System eighth edition). Corrected calcium levels are reported at postoperative day 1, 3 months, and 12 months to reflect immediate, medium, and long-term hypoparathyroidism. Requirement for oral calcium supplementation or low parathyroid hormone (PTH < 1.6 mmol/L) level was used as surrogate

TABLE 1 Definitions of normocalcaemia, transient, and permanent hypocalcaemia

Classification	Corrected calcium level	PTH level
Normocalcaemia	Corrected calcium ≥ 2.1 mmol/L	Normal
Transient hypocalcaemia	Corrected calcium < 2.1 mmol/L, then normal at 12 mo	Normal at follow-up (3 or 12 mo)
Permanent hypocalcaemia	Corrected calcium < 2.1 mmol/L at 12 mo or requiring supplemental calcium and vitamin D. Corrected calcium < 2.1 mmol/L at 3 mo AND low serum PTH	PTH < 1.6 mmol/L at follow-up

Abbreviations: PTH, parathyroid hormone.

TABLE 2 Patient and surgical characteristics

Characteristic (n = 30)		Statistic						
Age at operation, mean ± SD		68.3 ± 9.05						
Partial pharyngectomy + total laryngectomy, no. (%)		8 (27)						
Total pharyngolaryngectomy, no. (%)		22 (73)						
Anatomical location of primary tumor								
Glottis, no. (%)		2 (7)						
Hypopharynx, no. (%)		19 (63)						
Oropharynx, no. (%)		1 (3)						
Subglottis, no. (%)		2 (7)						
Supraglottis, no. (%)		4 (13)						
Thyroid, no. (%)		2 (7)						
Primary	NX	N0	N1	N2a	N2b	N2c	N3a	N3b
T1	0	0	0	0	0	0	0	0
T2	0	0	0	0	0	0	0	0
T3	0	1	1	0	2	1	0	0
T4	0	0	1	1	1	0	1	0
Recurrent	NX	N0	N1	N2a	N2b	N2c	N3a	N3b
rT1	1	0	0	0	0	0	0	0
rT2	0	3	0	0	0	1	0	0
rT3	2	3	0	0	2	1	0	0
rT4	4	3	0	0	0	1	0	1
Total	10	9	3	0	3	3	0	2
Total thyroidectomy, no. (%)		2 (7)						
Hemithyroidectomy, no. (%)		17 (57)						
Neck dissection, no. (%)		20 (67)						
Reconstruction, no. (%)		26 (87)						
Salvage surgery		22 (73)						
Previous chemotherapy, no. (%)		8 (27)						
Previous radiotherapy, no. (%)		19 (63)						
Previous surgery, no. (%)		3 (10)						
Preservation of parathyroid gland, no. (%)		24 (80)						
Autotransplantation of parathyroid gland, no. (%)		6 (20)						
Pathology, no. (%)								
Mucosal SCC		28 (93)						
Anaplastic thyroid carcinoma		1 (3)						
Hurthle cell carcinoma		1 (3)						
Corrected calcium (mmol/L), median (IQR)								
Day 1		2.19 (2.14-2.19)						
Discharge		2.34 (2.25-2.34)						
1 year		2.36 (2.17-2.37)						
PTH (pmol/L), mean ± SD		2.1 ± 2.47						
Length of stay, median (IQR)		33 (16-59)						

Abbreviations: IQR, interquartile range; no., number; SCC, squamous cell carcinoma.

markers to characterize hypocalcaemia if serum levels were unavailable. All data were collected using Microsoft Excel (Microsoft, Redmond, Washington). Categorical data were compared using the chi-squared test, or Fisher's exact test as appropriate and were

performed in R program.⁸ An alpha level less than 0.05 was considered significant. Normality was determined using Shapiro-Wilk test. Normally distributed data are expressed as mean ± SD, non-normally distributed data are expressed as median (interquartile range).

TABLE 3 Rates of transient and permanent hypocalcaemia by subgroup

Characteristics	All patients (n = 30)	Total pharyngolaryngectomy (n = 22)	Partial pharyngectomy + total laryngectomy (n = 8)	P value
Transient Hypocalcaemia, no. (%)	4 (13)	3 (14)	1 (13)	0.095
Permanent Hypocalcaemia, no. (%)	3 (10)	3 (14)	0 (0)	0.54

Note: Groups were statistically compared when separated into total and partial pharyngectomy groups.

2.5 | Classification of hypocalcaemia

Hypocalcaemia was defined by local pathology thresholds of serum corrected calcium level less than 2.1 mmol/L. Normocalcaemia was considered as corrected calcium >2.1 mmol/L. Transient hypocalcaemia was defined as corrected calcium <2.1 mmol/L at any time during the postoperative period that subsequently normalized (following temporary supplementation of calcium and vitamin D analogs) on follow-up bloods. Permanent hypocalcaemia was considered as (1) corrected calcium level below 2.1 mmol/L at 12 months follow-up, OR (2) requirement for long term supplementation at 12 months, OR (3) hypocalcaemia at 3 months (with low PTH <1.6 mmol/L), as per Kazaure and Sosa³ (Table 1).

3 | RESULTS

Thirty patients were included in this study. Baseline demographic, surgical, and calcium data can be seen in Table 2. Hypopharyngeal primary subsite location was the most common (n = 19, 63%), followed by supraglottis (n = 4, 13%) (Table 2). Summary of T and N staging are included in Table 2 below primary location, where they are reported as recurrent TNM staging in salvage, and primary TNM staging in primary cases (AJCC Staging System eighth edition). A majority of patients underwent total pharyngolaryngectomy (n = 22, 73%) and 8 (27%) partial pharyngectomy with laryngectomy. A limited number of patients underwent total thyroidectomy (n = 2, 7%) in comparison to hemithyroidectomy (n = 17, 57%). Most (n = 20, 67%) underwent concomitant neck dissection, and 87% (n = 26) had subsequent reconstruction of their defect. Parathyroid gland preservation was predominantly performed (n = 24, 80%), with 6 (20%) patients undergoing autotransplantation. The median length of stay (LOS) was 33 days (16 to 59). A majority of patients had salvage therapy (n = 22, 73%), with radiotherapy as the most common preoperative therapy (n = 19, 63%). A limited number of patients had previous chemotherapy (n = 8, 27%) or surgery (n = 3, 10%) prior to this procedure. Mucosal squamous cell carcinoma (SCC) was the most prevalent pathology (n = 28, 93%), followed by Hurthle cell carcinoma (n = 1, 3%), and anaplastic thyroid carcinoma (n = 1, 3%). Median corrected calcium level was 2.19 (2.14-2.19) on day 1 following surgery and was statistically lower than calcium levels on discharge ($P < 0.001$). The overall rate of transient and permanent hypocalcaemia was 13% (n = 4) and 10% (n = 3), respectively (Table 3). Total

TABLE 4 Characteristics of patients with transient and permanent hypocalcaemia

Characteristics	Transient hypocalcaemia (n = 4)	Permanent hypocalcaemia (n = 3)
Age at operation, mean \pm SD	71.4 \pm 10.2	68.1 \pm 10.1
Partial pharyngectomy + total laryngectomy, no. (%)	1 (25)	0 (0)
Total laryngopharyngectomy, no. (%)	3 (75)	3 (100)
Total thyroidectomy, no. (%)	1 (25)	0 (0)
Hemithyroidectomy, no. (%)	1 (25)	1 (33)
Neck dissection, no. (%)	3 (75)	2 (66)
Reconstruction, no. (%)	4 (100)	2 (66)
Salvage surgery, total no. (%)	3 (75)	3 (100)
Previous chemotherapy, no. (%)	1 (25)	1 (33)
Previous radiotherapy, no. (%)	3 (75)	2 (66)
Previous surgery, no. (%)	1 (25)	1 (33)
Preservation of parathyroid gland, no. (%)	3 (75)	2 (66)
Autotransplantation of parathyroid gland, no. (%)	1 (25)	1 (33)
Pathology, no. (%)		
Mucosal SCC	3 (75)	2 (66)
Anaplastic thyroid carcinoma	1 (25)	0 (0)
Hurthle cell carcinoma	0 (0)	1 (33)
Corrected calcium (mmol/L), median (IQR)		
Day 1	2.08 (2.06-2.11)	2.06 (1.91-2.11)
Discharge	2.31 (2.11-2.39)	2.16 (2.04-2.36)
PTH (pmol/L), mean \pm SD	NA	0.4 \pm 0.3
Length of stay, median (IQR)	42 (22-65)	40 (31-75)
Long term calcium replacement, no. (%)	0 (100)	3 (100)

Abbreviations: IQR, interquartile range; no., number; SCC, squamous cell carcinoma.

pharyngolaryngectomy patients had transient and permanent hypocalcaemia rates of 14% (n = 33) and 14% (n = 3), with partial pharyngectomy patients experiencing a transient rate of 13% (n = 1),

and permanent rate of 0% ($n = 0$). Rates did not significantly differ between operative subgroups.

Table 4 demonstrates demographical, surgical and calcium data for patients in transient and permanent hypocalcaemia subgroups ($n = 4$, $n = 3$). All ($n = 3$, 100%) patients in the permanent subgroup underwent surgery for salvage therapy, compared to 75% ($n = 3$) of the transient subgroup. Hemithyroidectomy and neck dissection rates were similar, and reconstruction did not occur in 1 patient with permanent hypocalcaemia. Preservation of the parathyroid gland was performed more commonly to autotransplantation in both groups. Length of stay was similar (41.5 IQR: 21.5 to 65 vs 40 IQR: 30.5 to 74.5, $P = 0.85$). Calcium levels were lower day 1 following surgery in both groups in comparison to discharge, but not significantly so. Most patients had SCC, with 1 patient in the transient subgroup undergoing surgery for anaplastic thyroid cancer, and 1 patient in the permanent group for Hurthle cell carcinoma.

4 | DISCUSSION

Postoperative hypocalcaemia is common following total pharyngolaryngectomy. Published rates of hypocalcaemia following pharyngolaryngectomy are variable, ranging between 15% and 65%.^{1,5,6} However, this study of 30 pharyngolaryngectomy patients demonstrates that lower rates of transient (13%) and permanent (10%) hypocalcaemia are achievable.

Definitions of hypocalcaemia are variable in the literature, with authors utilizing various corrected calcium cut-offs,^{4,6,9} parathyroid hormone (PTH) levels,¹⁰ or requirement for calcium and vitamin D supplementation.^{3,5} Further, the duration of permanent hypocalcaemia has differed in the literature between 6 and 12 months.^{3-5,11} Our approach was to utilize local definitions of hypocalcaemia (based upon corrected calcium). A lower threshold (<2.0 mmol/L) would result in a reduction of clinically relevant reported hypocalcaemia rates in this series.

Previous authors have identified various surgical risk factors for postoperative hypocalcaemia; including the extent of thyroid resection,^{1,4,5,12,13} bilateral neck dissection, salvage surgery,⁴⁻⁶ and resection of paratracheal lymph nodes.^{1,14} Hypoparathyroidism occurs due to inadvertent removal or devascularization of the gland during surgery. Central neck dissection places the parathyroid gland and its blood supply most at risk. In our cohort, hemithyroidectomy was preferred to total thyroidectomy (57% vs 7%), alongside preservation of the parathyroid gland or autotransplantation into ipsilateral sternocleidomastoid muscle. Historically, parathyroid autotransplantation has been avoided in head and neck cancer given the fear of invasion of the thyroid and parathyroid gland with metastatic disease. Harrison et al¹⁵ suggested this technique be more widely adopted in extensive hypopharyngeal surgery with Abd Elmaksoud et al¹⁶ demonstrating its success in 26 patients whom underwent total thyroidectomy and parathyroid autotransplantation with concurrent resection of extensive hypopharyngeal and laryngeal carcinoma. All included patients had restoration of normal PTH function and

normocalcaemia by the fourth postoperative week, with 1 patient having graft failure, and 2 patients excluded due to parathyroid gland invasion (prior to autotransplantation).¹² Our rates of transient and permanent hypocalcaemia (13%, 10%) are supportive of preservation or autotransplantation of the parathyroid gland (Table 3). Ipsilateral hemithyroidectomy in advanced hypopharyngeal and laryngeal cancer is supported by literature demonstrating superior oncological control.^{12,17} Basheeth et al⁶ also demonstrated a significant relationship between tumor stage (pT4) and hypocalcaemia ($P = 0.05$), but not with extent of thyroidectomy or pharyngectomy, while others have suggested pharyngectomy as a risk.⁵ Comparatively, rates in the total and partial pharyngectomy subgroups reveal a higher permanent and transient hypocalcaemia rate for those undergoing total pharyngectomy. This finding is supported by Clark et al,¹ where partial pharyngectomy patients had a hypocalcaemia rate of 38%, compared to 65% in the total (circumferential) pharyngectomy subgroup ($P < 0.001$).

Total and hemithyroidectomy were performed at similar rates in both hypocalcaemia groups (Table 4), with high concurrent rates of neck dissection and reconstruction in both. All permanent patients underwent salvage therapy, most commonly following radiotherapy. Radiotherapy may be a risk factor, previous studies indicating a higher risk of hypoparathyroidism than surgery alone (85% vs 63%, $P < 0.05$).¹⁸

The primary limitation to this study is its retrospective study design, and limited power due to modest study sample size. Our aim was to present data from the experience of a single institution with a standardized approach performed by a single surgeon, but further studies would benefit from interinstitutional collaboration.

5 | CONCLUSION

Hypocalcaemia is common after laryngectomy with total or partial pharyngectomy. Transient and permanent hypocalcaemia rates may be reduced by routine preservation or autotransplantation of parathyroid glands intraoperatively.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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