Intraoperative Parathyroid Gland Visualization UsingIndocyanine Green Autofluorescence for Prevention of Hypoparathyroidism During Total Thyroidectomy

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Abstract

Introduction: Thyroidectomy requires careful attention to the identification and intraoperative preservation of the parathyroid glands. This study aimed to determine if combining near-infrared fluorescent imaging with intraoperative parathyroid gland indocyanine green angiography could aid in the identification and preservation of parathyroid glands during total thyroidectomy. **Patients and Methods**: This study is a prospective, randomized double blinded controlled clinical trial, conducted on 66 patients eligible for total thyroidectomy. Hypoparathyroidism, both temporary and permanent, after surgery was the primary endpoint (PTH < 12 pg/mL). The secondary outcomes included serum calcium level, the number of autotransplanted PGs, and the number of PGs preserved in situ. The prevalence of complications including RLNP and hematoma were also recorded. **Results**: Hypoparathyroidism was more significantly encountered in the control group, compared to ICG group (36.4% Vs 15.2%, P=0.041). Parathyroid glands were more significantly preserved in situ in ICG group, compared to the control group (1.83 Vs 1.14, P=0.001). On postoperative day 3, parathyroid hormone level in the ICG group was considerably greater than in the control group (24.81±6.34 pg/mL vs. 17.83± 6.32 pg/mL, P= 0.012). **Conclusion:** The findings of our study demonstrated that intraoperative indocyanine green angiography of the parathyroid glands using near-infrared fluorescence imaging is a reliable and safe procedure. This method allows for more accurate detection and evaluation of PG perfusion.

Key words: Indocyanine green, Thyroidectomy, Hypocalcemia

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Introduction

Complications following a thyroidectomy range from mild to life-threatening and have included hemorrhage and vocal cord palsy. Nonetheless, hypocalcemia is still the leading consequence of thyroid surgery. Temporary hypoparathyroidism after surgery occurs in 27% of patients (19%-38%) while persistent hypoparathyroidism occurs in 1% of patients (0-3%).**[1]** Hypocalcemia is a consequence of parathyroid gland (PG) trauma or devascularization. The PG'slittle size and erratic placement are just two examples. In addition, calcitonin oversecretion from thyroid management during surgery and hungry bone syndrome can play a role in exacerbating this complication.**[2]** In addition, with only a slight drop in serum calcium levels, hypocalcemia may not even be noticeable. Muscle spasms, paresthesia, Chvostek's sign, and Trousseau's sign are all possible though. Hospital stays and medical bills are both affected when people have transient hypoparathyroidism. Those with permanent hypoparathyroidism will need to take medicine for the rest of their lives. Thyroidectomy has traditionally required careful attention to the identification and intraoperative preservation of the parathyroid glands (PGs).**[3]** Traditional methods for identifying and evaluating PGs rely heavily on the surgeon's ability to visually recognize the PG's anatomical position and outward appearance (color, shape, etc.). However, it is challenging to completely safeguard the PGs due to the fact that, this visual assessment is frequently affected by variables like as the surgeon's experience, intraoperative hemorrhage, ectopic PGs, etc. The use of near-infrared (NIR) fluorescence imaging with indocyanine green (ICG) angiography has been increasingly commonplace as a means to detect PG and evaluate their vascularization in recent years.**[4]** Strong fluorescence is seen on indocyanine green angiography because more blood vessels can be found in the PG than in the surrounding tissues.**[5]** This study set out to determine if combining NIR fluorescent indocyanine imaging with intraoperative parathyroid gland ICG angiography could aid in the identification and preservation of parathyroid glands during total thyroidectomy, hence decreasing the risk of postoperative hypocalcemia.

Methods

Study design

This clinical trial is a randomized, controlled, double-blind study with a prospective design. Sixty patients who had undergone complete thyroidectomy were analyzed to learn more about post-op hypocalcemia, how often it occurs, and how Indocyanine Green Fluoroscopy can help. Between January 2022 and September 2022, researchers from Al-Azhar University Hospital gathered data for this study. Each participant gave written informed permission and received approval from a local ethics committee.

Inclusion criteria

- People of both sexes, ranging in age from 21 to 60
- Both new and recurrent goiters can result from benign thyroid lesions.
- Serum calcium, parathyroid hormone, and vitamin D levels were within acceptable ranges

Exclusion criterions

- • A history of parathyroidectomy or neck dissection.
- Renal or hepatic impairment
- Malignant thyroid disease
- Preoperative calcium supplementation or use of drugs known to influence blood calcium metabolism, such as hormone replacement therapy for postmenopausal women, anabolic agents, or thiazide-type diuretics, may increase the risk of complications after surgery.
- cases with hyperparathyroidism.

Sample size calculation

Sample size was calculated using MedCalc program version11.3.0.0. to establish the representative sample and assure the validity of the results. The effect size was estimated based on the data revealed by (Yin et al, 2022), who reported that the prevalence of transient hypoparathyroidism was 43.3% in the control group and 27.8% in the indocyanine. Adjusting the confidence intervalto 95%; power 80% and ratio amongst groups to 1:1; a sample of 60 cases was found reliable. Estimating a dropout ratio of 10%, we finally included 66 cases.

Randomization

To allocate individuals, a computer-generated randomization procedure was utilized. The researchers tested a telephone-mediated central allocation strategy for allocation concealment.

Procedure

Preoperative Evaluation

A complete history is taken, including any history of manifest tetany (carpopedal spasm, stridor).

2. Full physical examination:

General: This includes the build, weight, pulse rate, and blood pressure.

Local: The objective of inspection, palpation, percussion, and auscultation is to evaluate the size and consistency of the gland, its mobility or fixation to the surrounding structures, and the presenceof a palpable thrill or audible murmur.

3. Laboratory observations: Thyroid functions, calcium, PTH, CBC, LFTs, coagulation profile, and fasting glucose were tested from the blood samples collected..

4. Radiological investigations:

i) Neck Ultrasonography: This screening was the first step for each patient. Being checked out by a seasoned sonographer was a must so that accurate data could be extracted regarding the thyroidcondition.

ii) Thyroid Scan: This was performed on thyrotoxic patients.iii)Plain X- ray chest P-A view.
IV) Neck CT with contrast: catered to individuals who had retrosternal extention.

5. Pathological investigations: Those who had a single thyroid nodule or a multinodular goiter in which one nodule was particularly large had FNAC.

6. Indirect laryngoscopy: All patients had their vocal cord mobility evaluated.

Patients with thyrotoxicosis were preoperatively prepared with:

- Bed rest.
- 1 mL of Lugol's iodine daily for 10 days prior to surgery.
- Propranolol (Inderal): 10-40 mg t.d.s.
- Antithyroid medicines for slow and, on occasion, quick preparation.

During rest, the patient's heart rate should be about 70 beats per minute, and there should be nosigns of thyrotoxicosis, especially palpitations, before surgery is performed.

Imaging system

The autofluorescence of the parathyroid glands was measured with an indocyanine green/near- infrared endoscopic system (Karl Storz, Tuttlingen, Germany). The system is made up of a HopkinsTM II, Karl Storz 10-mm 0-degree indocyanine green laparoscope connected to a high- end full high-definition camera system (H3-Z 3-Chip Full HD camera, Karl Storz;).

Surgical technique

The patient lies supine on the operative table, which tilted 15 degrees upward at the head. A sandbag pillow is placed between the shoulder blades with the neck extended, thus making the gland more prominent. All patients in the first group had ICG angiography during the operation. All patients were put under general anesthesia and intubated with a breathing tube. One centimeter below the cricoid cartilage, a 4- to 5-centimeter-long Kocher transverse collar incision was performed. All the way down to where the thyroid gland was visible, the strap muscles were cut along the middleDissection of the neck was performed to locate the internal jugular vein and nerves, which required separating the sternohyoid muscles from the underlying sternothyroid muscle. To avoid devascularizing the parathyroids or injuring the recurrent laryngeal nerves, As close to the surface of the thyroid as was physically possible, the inferior thyroid arteries were dissected and divided. It is important to locate the recurrent laryngeal nerve when it enters the tracheoesophageal groove between the branches of the inferior thyroid artery. Behind the inferior cornu of the thyroid cartilage is a passageway that the nerve uses to enter the larynx. Suction drainage of the deep cervical cavity ensures complete hemostasis and allows for a successful wound closure. All thyroid tissue samples were histoanalyzed.

The standard ICG formulation, 15 mg, was injected intravenously by the anesthesiologist. The parathyroid glands soaked up the dye in within two minutes, and it shone brightly for the next 15 after that. The surgical assistant started recording the procedure immediately following the ICG injection. The parathyroid's FI in ICG angiography is dependent on how much ICG is absorbed by the glandThe parathyroid's ability to absorb the dye has to do with the endocrine system's rich blood supply, right? Thus, parathyroid FI is indicative of the organ's degree of vascularization. Several shades of grey can be used as a benchmark for various degrees of parathyroid function in ICG angiography applications. After completing an ICG angiogram, the parathyroid glands were given a score between 0 and 2 on the FI scale. Weak FI is represented by a score of 0, moderate FI by 1, and strong FI by 2. Surgeons will perform parathyroid autotransplantation on glands that were deemed vascularized during ocular inspection but devalued upon ICG angiography.

Blood perfusion was assessed visually by looking for PGs in situ in the control group. Autotransplantation into the sternocleidomastoid muscle was performed using PGs from both groups with an ICG or visual score of 0 as well as PGs from resected tissues.

Follow up

All patients were followed up at 1, 3, and 6 months. At each visit, clinical examination, serum calcium level, PTH and TSH were carried out.

Evaluation of recurrent laryngeal nerve status just after surgery by an otolaryngologist was done to asses vocal cord mobility by direct laryngoscopy. The patient is considered to have temporary recurrent laryngeal nerve palsy (RLNP) when there is hoarseness of voice associated with evident vocal cord paralysis at laryngoscopy during the first 6 months; If symptoms last longer than six months, we consider the patients developed permanent RLNP.

Evaluation of the parathyroid function was checked immediately at the third postoperative day and every follow-up visit by measurement of serum calcium and PTH levels. A surgical hypoparathyroidism diagnosis was made when the PTH level dropped below 12 pg/mL. Definition of hypocalcemia: less than 8.0 mg/dl calcium in at least two consecutive samples over the course of three days. Hypoparathyroidism was classified as either transitory (reversing within 6 months) or permanent (persistently persisting beyond 6 months). The hypocalcemic patient was given oral calcium supplements (1-4 g daily). When serum calcium levels dropped below 7.5 mg/dl, vitamin D was administered. Serum calcium levels will remain elevated till supplementation is discontinued.

Postthyroidectomy bleeding is defined as a hematoma that requires immediate wound exploration and good hemostasis.

Outcome Assessment

Hypoparathyroidism, both temporary and permanent, after surgery was the primary endpoint. (PTH < 12 pg/mL).

The secondary outcomes included serum calcium level, the number of autotransplanted PGs, and the number of PGs preserved in situ. The prevalence of complications including RLNP and hematoma were also recorded.

Statistical Analysis

SPSS version 23.0 considered for analysis. Presentation was based on the type, normality and distribution of the variables. Kolmogorov test was first applied. Normally distributed variables, explicated mean and standard deviation, whilst non-normal data explicated median and IQR. The Mann Whitney U test and the student-t test were mentioned in this study for inter-group analysis regarding the non-parametric and parametric numerical variables respectively. In addition, categorical variables were analyzed using the Chi-square (x)2 test. A point of 0.05 was set as the significant level.

Results

Operative and Demographic Characteristics

A total of 66 patients were enrolled in this study. Figure 1 represented the flow of the study process. Patients demographics were similar between the two group with no statistically significant comparison, regarding age, gender, and body mass index (BMI). No significant difference was reported regarding the indication of thyroidectomy and the duration of surgery as revealed in Table 1.

Outcomes

Hypoparathyroidism was more significantly encountered in the control group, compared to

ICG group (36.4% Vs 15.2%, P=0.041). Permanent hypoparathyroidism was not detected in either groups (Table 2). In addition, autotransplantation of the parathyroid glands was performed in 6 cases (in 4 cases – one gland, in one case – 2 glands, in one case – one gland) in the control group, based on visual inspection of the gland perfusion. On the other hand, autotransplantation in ICG group was performed in 13 patients (in 9 cases – one gland, in 3 cases – two, in one case – 3). Importantly, the total number of autotransplanted PGs was higher in ICG group, compared to the control group, with non-significant comparison (P=0.293) (Table 2). Moreover, PGs was more significantly preserved in situ in ICG group, compared to the control group (1.83 Vs 1.14, P=0.001) (Table 2).

On postoperative day 3, and then again at 1 month, 3 months, and 6 months, serum calcium and PTH levels were measured in all patients. Serum calcium levels showed no discernible variation across the study groups. We assessed parathyroid function using PTH levels since postoperative serum calcium level changes tend to lag and are potentially impacted by calcium supplementation across participants. On postoperative day 3, PTH levels in the ICG group were considerably greater than in the control group (24.81±6.34 pg/mL vs. 17.83± 6.32 pg/mL, P= 0.012) (Table 3).

Clinically, in the control group, two cases showed classic signs of hypocalcemia, including finger and circumoral paraesthesia, which improved by oral calcium 1 gm supplementation. Indeed, most patients in the two groups had suptle symptoms of hypocalcemia due to standard oral calcium supplementation.

One patient (3.03%) in each group suffered from temporary unilateral RLNP, which improved 1 month postoperatively. Bilateral RLNP was not reported in both groups. One patient suffered from postthyroidectomy bleeding, managed by urgent wound reexploration and ligation of the bleeding vessels (Table 4).

Discussion

The most common long-term effect of a thyroidectomy is hypoparathyroidism. There is currently no accepted method for identifying and protecting parathyroid glands and their blood supply during thyroidectomy.[6] The survival of parathyroid glands in surgery depends on both their blood supply and their location. Nonetheless, the large degree of anatomical variance calls for a surgeon with a great deal of experience and flexibility. In addition, 8.2% of parathyroids get their blood supply from the thyroid gland, making preservation much more of a challenge. [1] So, even the most skilled surgeons will occasionally make an error that results in an unintentional excision or devascularization.

Recent years have shown promise for the use of (NIFI), which includes imaging with both PG autofluorescence (AF) and indocyanine green fluorescence (ICGF) to safeguard PGs during thyroid surgery. While AF can help in finding the PGs, it does not reveal whether or not the glands will survive. [7] Hence, AF and ICG can shed light on the vascularization and activity of the glands in addition to their anatomy. In the present investigation, AF imaging was employed to recognize and localize PGs prior to any initial dissection of the thyroid. Next, following the removal of the thyroid gland, ICG imaging was used to check the perfusion of the PGs and direct their autotransplantation. Our findings demonstrated that ICG-AF during complete thyroidectomy considerably reduced the frequency of temporary postoperative hypoparathyroidism and improved the identification of parathyroid glands (PGs) in comparison to standard naked eye surgery. In addition, the number of PGs preserved in situ exceeded that of the control group. This approach enhances the capacity to locate PGs and rises the likelihood of maintaining the glands in situ that could be the fundamental reason for the decreased frequency of temporary postoperative hypoparathyroidism. In addition, this study revealed that evaluation of gland vascularity by ICG was more reliable than visual inspection. Fortuny et al. found that patients were more likely to have normal postoperative PTH levels if they had one PG with good perfusion (measured as an ICG score of 2). Two vascularized glands, as seen on ICGF, are necessary for adequate parathyroid activity, as reported by Rudin et al. [9] One possible explanation for this difference is the subjective nature of determining an individual's ICG score.

This study indicated that the number of PGs autotransplanted was higher in the ICG group, but the difference was not statistically significant. Rudin et al. discovered that when evaluating PG perfusion with ICGF, autotransplantation occurred considerably more often than in the non-ICGF group. [9] They reasoned that ICGF could help steer autotransplantation in the right direction. However, a randomized clinical trial involving multiple centers found that autotransplantation occurred in much fewer individuals in the AF group than in the control group without AF. [10] They speculated that AF might aid in the protection of the PGs during complete thyroidectomy. Yet, there is no assurance that it will flourish in its new environment after being replanted. So, dissecting the tissue around the parathyroid gland is the ideal way to employ this imaging technique to guarantee the gland receives adequate blood flow.

There were some caveats to this study. To begin, the use of ICG-AF to evaluate PGs perfusion is highly subjective. One potential approach that could yield more reliable results is a quantitative analysis of the fluorescence intensity. Second, although the cost of the imaging system is considerable now, it will become more cost-effective because it can be used for multiple surgeries.

Conclusion

Intraoperative indocyanine green angiography of the parathyroid glands using near-infrared fluorescence imaging is a reliable and safe procedure. This method allows for more accurate detection and evaluation of PG perfusion. ICG imaging provides a more objective method than ocular inspection for determining whether or not the PG requires autotransplantation.

Table 1. Patient demographic and baseline characteristics.

Demographic data	ICG (n=33)	Control (n=33)	p-value
Age (years)	42.15±11.31	44.61±9.61	0.461
Gender n (%)			
Male	8 (24.2)	9 (27.3)	0.328
Female	25 (75.8)	24 (72.7)	
BMI (kg/m^2)	27.16±3.72	28.32±4.27	0.641
Indications for surgery n (%)			
Multinodular goiter	23 (69.7)	25 (75.8)	0.316
Toxic nodular goiter	8 (24.2)	7 (21.2)	
Grave's disease	2 (6.1)	1 (3.0)	
Duration of hospital stay (days)	2.81±1.31	2.58±1.42	0.528

Table 2. Outcomes in the two study groups.

	ICG (n=33)	Control (n=33)	p-value
Transient hypoparathyroidism	5 (15.2)	12 (36.4)	0.041
Permanent hypoparathyroidism	0	0	
PGs preserved in situ	1.83±0.41	1.14±0.52	0.001
Autotransplanted PGs (Total cases)	13 (39.4)	6 (18.2)	0.531
1 PGs	9 (27.3)	4 (12.1)	
2 PGs	3 (9.1)	1 (3.0)	
3 PGs	1 (3.0)	1 (3.0)	
Total N of Autotransplanted PGs	18	9	0.293

Data presented as n (%), mean±SD

Table 3. Distribution of PTH and calcium serum level during the follow up period.

	ICG (n=33)	Control (n=33)	p-value
PTH (pg/ml)			
Baseline	52.49±12.15	49.25±13.62	0.571
POD 3	24.81±6.34	17.83±6.32	0.012*
1 month	40.84±9.52	38.33±8.37	0.816
3 months	39.76±6.13	38.72±6.57	0.641
6 months	45.38±10.71	46.92±10.27	0.169
Calcium (mg/dl)			
Baseline	9.25±0.21	9.71±0.13	0.924
POD 3	8.93±0.15	8.87±0.14	0.575
1 month	9.35±0.10	8.82±0.25	0.218
3 months	9.15±0.14	8.93±0.11	0.955
6 months	9.11±0.15	9.24±0.31	0.528

* *p value, significant*

POD, postoperative day

Table 4. Comparison between the two study groups regarding complications.

	ICG (n=33)	Control (n=33)	p-value
Temporary unilateral RLNP	1 (3.03)	1 (3.03)	0.521
Permanent unilateral RLNP	0	0	
Bilateral RLNP	0	0	
Hematoma	1 (3.03)	0	0.318

RLNP, recurrent laryngeal nerve palsy

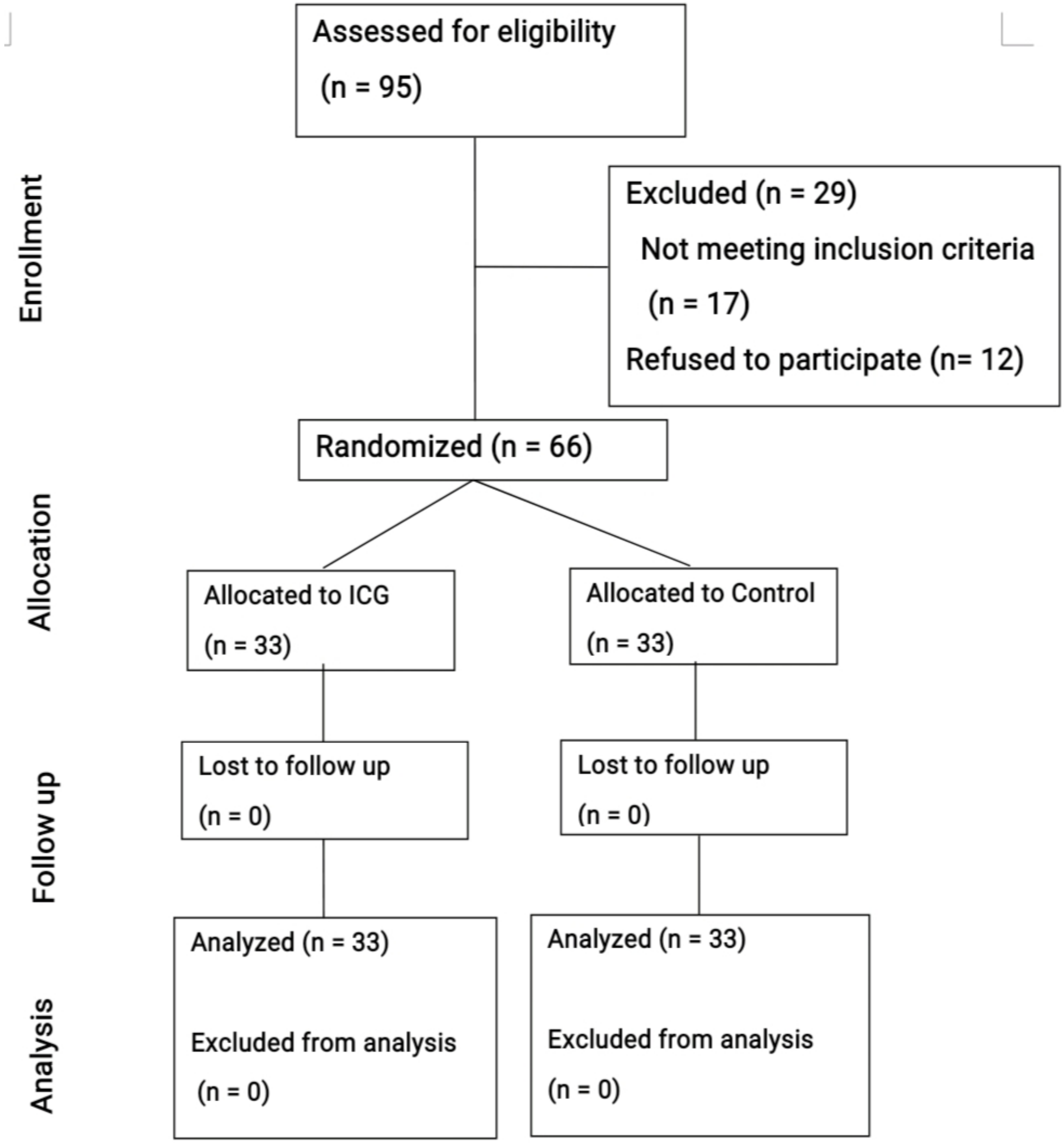

Figure 1. CONSORT flow diagram.

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