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ORIGINAL ARTICLE

A combined nano-carbon tracer and nano-fluorescence assay for parathyroid misresection reduction in thyroid surgery

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KEYWORDS

Nano-carbon tracer;
Nano-fluorescence assay;
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Abstract *Background:* In recent years, the incidence of nodular goiter and thyroid carcinoma (TC), as well as the amount of surgery, have been increasing simultaneously. To summarize the significance and experience of combined nano-carbon tracer and nano-fluorescence assay for parathyroid misresection reduction in thyroid surgery.

Methods: The data of patients who underwent thyroid surgery from November 2016 to July 2017 in the Thyroid Disease Diagnosis and Treatment Center of the Tenth People's Hospital of Tongji University were collected and divided into test group (combined nano-carbon tracer and nano-fluorescence assay method, 80 cases) and a control group (nano carbon tracer method, 80 cases). Comparison of the patient data and preoperative and postoperative blood calcium, blood phosphorus, PTH value in the control and test group was performed.

Results: No significant difference was found on gender, age, preoperative Calcium, Phosphorus, Magnesium and PTH, postoperative Calcium, Phosphorus and Magnesium was found in the control and test group (all the $p > 0.05$), whereas significant difference was found on the postoperative PTH between control and test group ($p < 0.001$). Moreover, significant reduced number of parathyroid misresection was found in the test group compared to the control group ($p = 0.003$). Significant difference could be found on pre- and postoperation data of blood Calcium, Phosphorus, Magnesium and PTH in both control and test group (all the $p < 0.05$).

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Conclusions: A combined nano-carbon tracer and nano-fluorescence assay can be used in thyroid surgery, which is helpful to distinguish parathyroid tissue, avoid accidental injury or missection of parathyroid gland as much as possible, and reduce the incidence of postoperative hypocalcemia.
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1. Introduction

In recent years, the incidence of nodular goiter and thyroid carcinoma (TC), as well as the amount of surgery, have been increasing simultaneously (Filetti et al., 2019). With the improvement of surgical skills and the development of surgical instruments, the mortality and nerve injury complications of thyroid surgery have decreased significantly (Raue and Frank-Raue, 2016). However, temporary or permanent hypocalcemia is still one of the most common postoperative complications (Del Rio et al., 2019). At present, there is still a lack of simple and effective clinical methods for early prediction of the occurrence of hypocalcemia, and the assessment system of the risk factors of its occurrence is still not perfect (Del Rio et al., 2019). Our hospital recently carried out a combined nano-carbon tracer and nano-fluorescence assay to avoid parathyroid tissue misresection during operation, and we also obtained the patient characteristic and blood Calcium, Phosphorus, Magnesium and PTH data to summarize experience and analysis. In order to promote this detection method, reduce the occurrence of postoperative hypoparathyroidism, and improve the quality of life of patients after surgery.

With the development of nanotechnology, carbon nanoparticles have been applied to tumor markers, such as breast and colorectal cancer (Jiang et al., 2015). The injected carbon nanoparticle suspension includes nanometer carbon particles with an average diameter of 150 nm (Wang et al., 2013). Due to permeability and molecular size; these particles do not enter the blood circulation and have no toxic side effects on the human body (Lin et al., 2021). Since 2007; China Food and Drug Administration approved the use of nano-carbon suspension in humans. Meanwhile; fluorescence-associated image-guided surgery has demonstrated significant potential to intraoperatively detect malignant tissues in endoscopic and robotic surgeries and distinguish tumor margins (Jensen et al., 2020; Zhou et al., 2021).

In this study, we aimed to identify the significance and experience of combined nano-carbon tracer and nano-fluorescence assay for parathyroid misresection reduction in thyroid surgery. We found that a combined nano-carbon tracer and nano-fluorescence assay can be used in thyroid surgery, which is helpful to distinguish parathyroid tissue, avoid accidental injury or missection of parathyroid gland.

2. Materials and methods

2.1. Subjects

The clinical data of 160 patients who underwent thyroid surgery at the Thyroid Disease Diagnosis and Treatment Center of the Tenth People's Hospital of Tongji University from November 2016 to July 2017 were collected. The combined nano-carbon tracer and nano-fluorescence assay was defined as test Group (80 cases), the case of using the nano carbon tracer negative imaging method to identify parathyroid glands was defined as the control group (80 cases). All cases are Papillary thyroid carcinoma (PTC) and central lymph node dissection was performed. The surgeons in the two groups are all senior doctors with professional skills of thyroid surgery, and Energy devices, such as Harmonic Focus Plus (Ethicon; ultrasonic scalpel; Harmonic) was used during the operation. This study was reviewed and approved by the Ethics Committee of Shanghai Tenth People's Hospital. All patients were provided with written informed consent before surgery were included in the present study.

2.2. Detection method

During the operation, the parathyroid glands are routinely exposed on the dorsal side of the thyroid gland based on clinical experience. In general, the upper parathyroid glands on the two sides are easier to distinguish, and the lower parathyroid glands are easily confused with fat or lymph node tissue, so the main diagnosis is for the lower parathyroid glands. A negative pressure maintained 22 gauge needle was used for the suspected parathyroid tissue puncture and repeated for 3 times (only one side of the parathyroid tissue is selected for each case) for tissue collection, and the tissue was then mixed the loading buffer solution to obtain the supernatant, followed by adding into sample testing holes. After the standing still for 10 min, the testing card was inserted into the machine for measurement. The system will automatically read the card and display the test result. The buffer test tube containing the puncture material was sent to the pathology department, and the professional pathologist will judge whether the tissue was enough to obtain a pathological examination. The Calcium, Phosphorus, Magnesium and PTH were analyzed (LABMED, China).

2.3. Data interpretation

According to the equipment instructions, the system gives the C value and T1 value, where C is the quality control parameter, if $C < 1000$, the measurement result was meaningless; if $C \geq 1000$, further analyze the T1 value, if $T1 < 20000$, it means the result was negative, and the tissue was not parathyroid tissue: If $T1 \geq 20000$, the result was defined as positive, and it meaned that the PTH content was high, and the tissue was considered as the parathyroid tissue.

2.4. Statistical analysis

The data from present study was analyzed by SPSS 19.0 statistical software package. The measurement data such as blood

calcium, blood phosphorus, blood PTH value between 2 groups were all used in mean ± standard deviation (SD), and the comparison was performed by *t* test; count data was expressed as number and percentage and compared by $\chi 2$ test. $P < 0.05$ indicates that the difference was statistically significant.

Table 1 Comparison of the patient characteristic and blood Calcium, Phosphorus, Magnesium and PTH data in control and test group.

	Control	Test	$\chi 2$ or t value	P value
Gender			1.290	0.256
Male	15	21		
Female	65	59		
Age	49.18 ± 13.07	51.45 ± 12.75	−1.114	0.267
Pre-				
Ca	2.34 ± 0.12	2.33 ± 0.13	0.862	0.390
P	1.11 ± 0.15	1.14 ± 0.15	−1.358	0.177
Mg	0.87 ± 0.06	0.87 ± 0.08	0.247	0.805
PTH	42.72 ± 13.53	42.85 ± 16.39	−0.056	0.955
Post				
Ca	2.09 ± 0.14	2.13 ± 0.15	−1.556	0.122
P	1.05 ± 0.25	1.04 ± 0.23	0.420	0.675
Mg	0.75 ± 0.07	0.77 ± 0.07	−1.164	0.264
PTH	14.42 ± 13.96	22.01 ± 15.55	−3.251	0.001
Parathyroid misresection			8.581	0.003
Yes	18	5		
No	62	75		

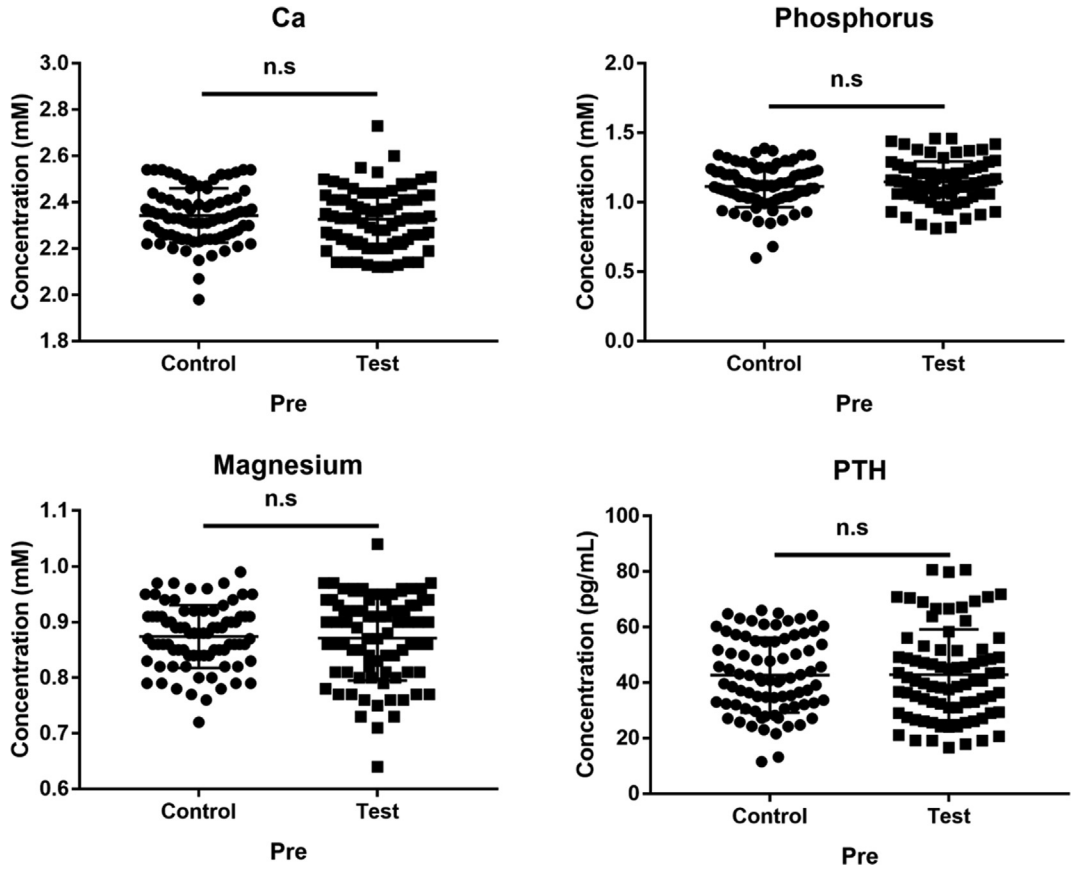

Fig. 1 No significant difference was found on preoperative Calcium, Phosphorus, Magnesium and PTHnd in the control and test group (all the $p > 0.05$).

3. Results

3.1. Comparison of the patient characteristic and blood Calcium, Phosphorus, Magnesium and PTH data in control and test group

The average duration of the operation is about 40–70 min, in which it will take a same duration in control and test group. And the test group take only 1 min to puncture for fluid testing. The images of the sampling and operation was shown (FigS1). As shown in Table 1 and Figs. 1 & 2, no significant difference was found on gender, age, preoperative Calcium, Phosphorus, Magnesium and PTH, postoperative Calcium, Phosphorus and Magnesium was found in the control and test group (all the $p > 0.05$), whereas significant difference was found on the postoperative PTH between control and test group ($p < 0.001$). Moreover, significant reduced number of parathyroid misresection was found in the test group compared to the control group ($p = 0.003$).

3.2. Comparison of pre- and postoperation data of blood Calcium, Phosphorus, Magnesium and PTH in control and test group

As show in Table 2 and Figs. 3 & 4, significant difference could be found on pre- and postoperation data of blood Calcium, Phosphorus, Magnesium and PTH in both control and test group (all the $p < 0.05$).

4. Discussion

Hypocalcemia is one of the common complications of thyroid surgery (Van Slycke et al., 2021). It is mainly caused by insufficient PTH secretion (Van Slycke et al., 2021). It is often caused by accidental resection of the parathyroid glands during the operation, parathyroid blood supply injury by surgical or thermal caused damage by energy devices (Sitges-Serra et al., 2018). According to reports in the literature, the incidence of temporary hypoparathyroidism after thyroid surgery ranges from 1.6 to 68% (Thomusch et al., 2018), while the incidence of permanent hypoparathyroidism is 2%-6% (Thomusch et al., 2018). Once permanent hypoparathyroidism occurs, the patient needs life-long drug treatment and regular follow-up, which often brings heavy medical burden and psychological pressure to the patient and also the difficulties faced in the clinical practice (Cirocchi et al., 2019). Hypocalcemia usually occurs 24 to 48 h after surgery, but it also occurs after 4 days after surgery (Dedivitis et al., 2017). It is difficult to predict the occurrence of hypocalcemia in the clinical practice (Dedivitis et al., 2017). In the past, the hospitalization time was long, and the blood calcium level can be continuously monitored after the operation thereby resulting fulfillment of

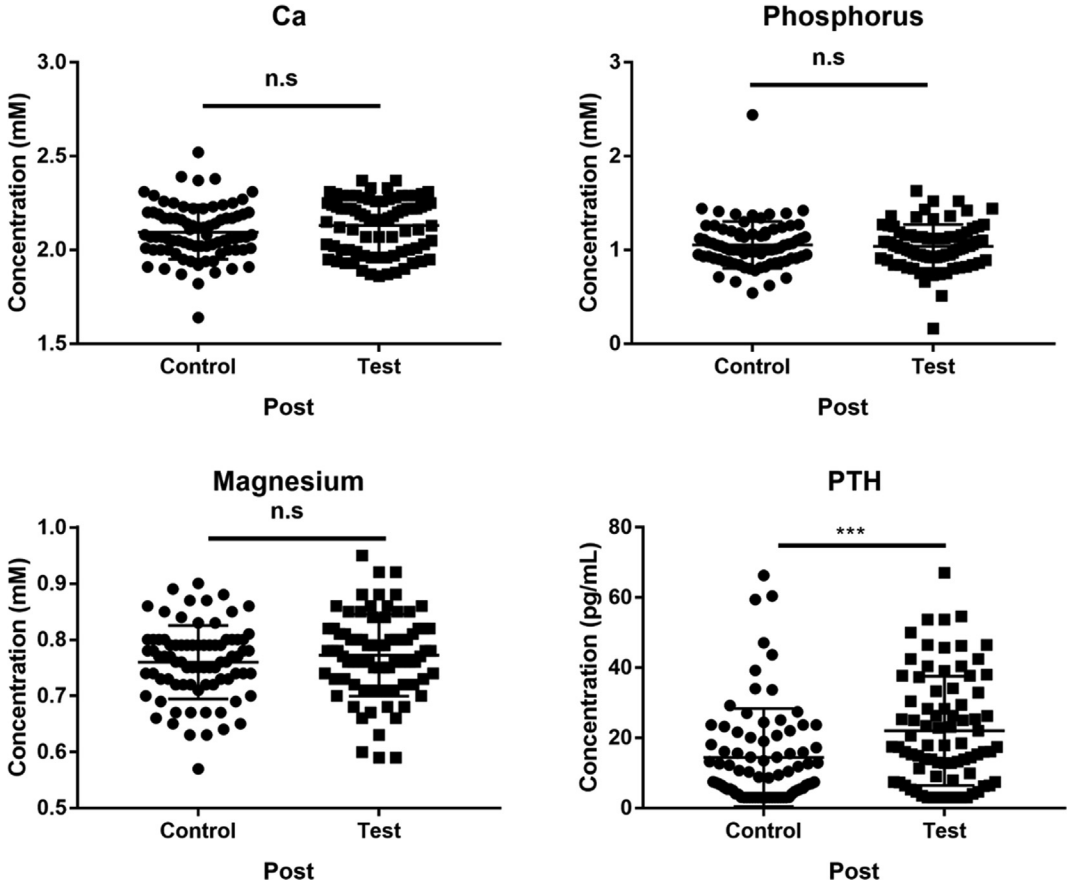

Fig. 2 No significant difference was found on postoperative Calcium, Phosphorus and Magnesium in the control and test group (all the $p > 0.05$), whereas significant difference was found on the postoperative PTH between control and test group ($p < 0.001$).

Table 2 Comparison of pre- and postoperation data of blood Calcium, Phosphorus, Magnesium and PTH in control and test group.

	Control			t value	P value	Test			t value	P value
	n	Pre	Post			n	Pre	Post		
Ca	80	2.34 ± 0.12	2.09 ± 0.14	20.164	0.000	80	2.33 ± 0.13	2.13 ± 0.15	7.629	0.000
P	80	1.11 ± 0.15	1.05 ± 0.25	2.190	0.031	80	1.14 ± 0.15	1.04 ± 0.23	4.928	0.000
Mg	80	0.87 ± 0.06	0.76 ± 0.07	18.322	0.000	80	0.87 ± 0.08	0.77 ± 0.07	17.837	0.000
PTH	80	42.72 ± 13.53	14.42 ± 13.96	13.100	0.000	80	42.85 ± 16.39	22.01 ± 15.55	9.490	0.000

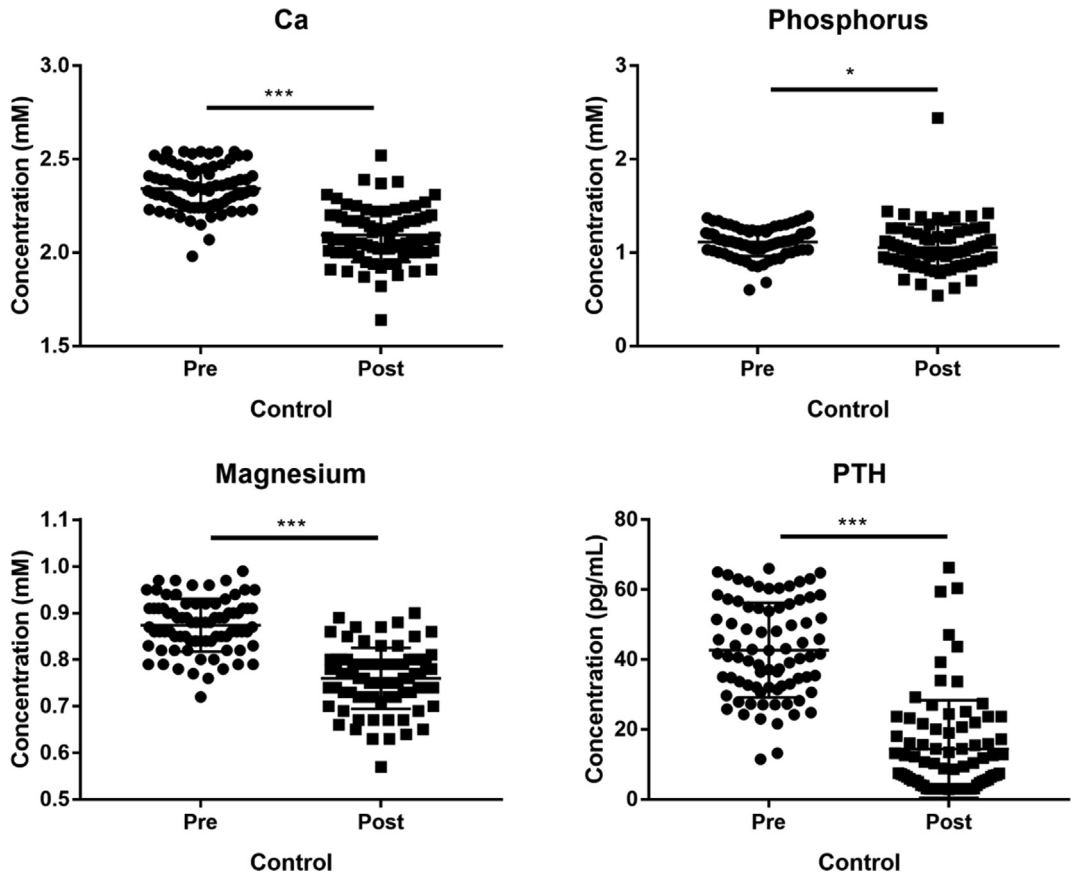

Fig. 3 Significant difference could be found on preand postoperation data of blood Calcium, Phosphorus, Magnesium and PTH in test group.

calcium supplement in time to prevent hypocalcemia (Dedivitis et al., 2017). At present, with the development of the modern concept of "rapid recovery", the length of hospital stay is getting shorter and shorter, especially with the rise of "day surgery" (Huang et al., 2021). Patients are often discharged after 1 to 2 days after surgery, and there may not be corresponding clinical manifestations of hypocalcemia within time after surgery (Iglesias and Diez, 2017). Therefore, the diagnosis is often not made in time. Failure to detect or predict hypocalcemia in time for corresponding treatment will inevitably bring about adverse consequences. In most cases, postoperative PTH can accurately predict blood calcium levels to determine whether hypocalcemia will occur (Caglia et al., 2017). However, the PTH value is not absolutely reliable. Nearly 14% of patients with PTH are at normal levels without the manifestations of hypocalcemia (Huang et al., 2021). Since the half-life of PTH is only 2 to 5 min, most scholars believe that rapid intact parathyroid hormone (iPTH) determination as early as possible after surgery is the best way to judge hypocalcemia, however it is difficult to achieve rapid iPTH measurement in most primary hospitals in China due to the expensive (Barczynski et al., 2007). How to effective prevent missection of parathyroid gland has been the major clinical concerns. It has been reported that nano-carbon and titanium clip were combined with labeling assisted surgery before neoadjuvant chemotherapy and radiotherapy in rectal cancer (Lin et al., 2020). Nano-carbon combined with titanium clip labeling was applied in robot-assisted laparoscopic transverse colon cancer surgery (Lin et al., 2021).

In the present study, the patient in the Control group only use nano carbon tracer. Nano carbon tracer is a commonly used staining agent in clinical practice (Ren et al., 2019). The

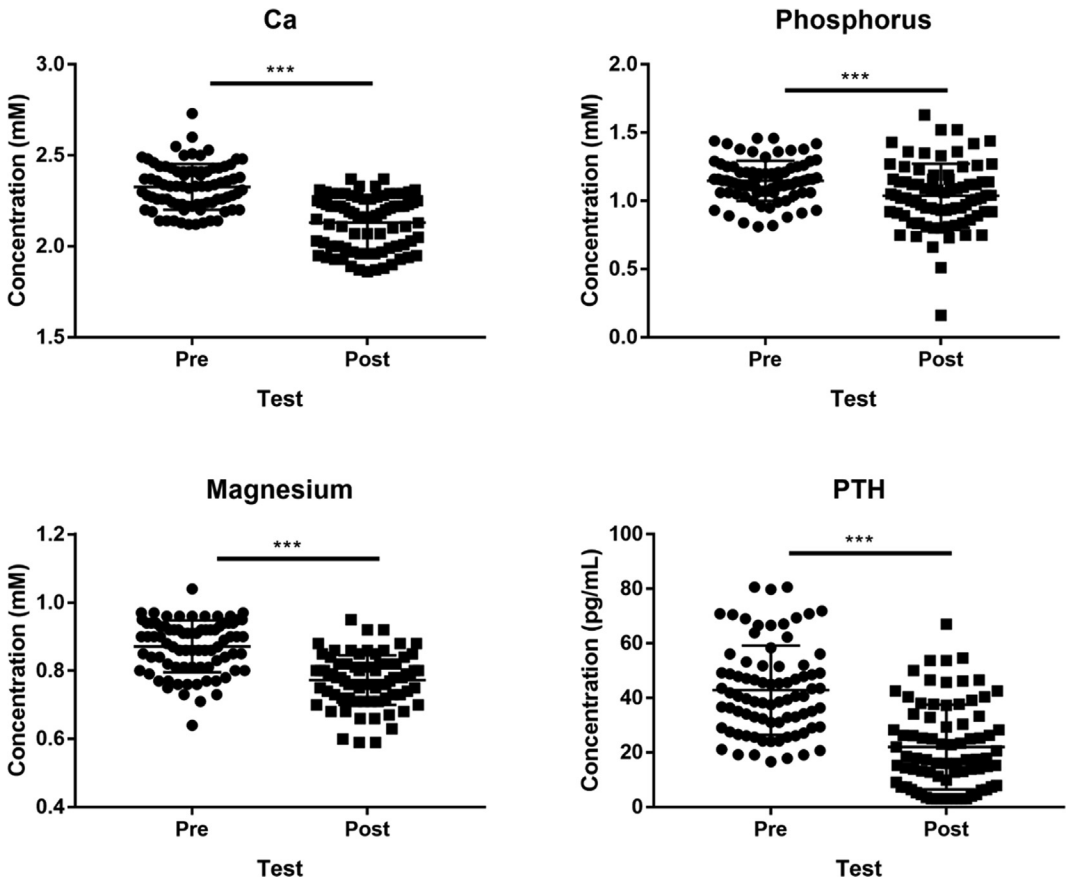

Fig. 4 Significant difference could be found on preand postoperation data of blood Calcium, Phosphorus, Magnesium and PTH in control group.

surgeon will inject a tracer into the thyroid during surgery (Ren et al., 2019). The thyroid and most of the lymph nodes will be stained (Ren et al., 2019). The parathyroid glands are not stained to help visually identify the thyroid, lymph nodes and parathyroid glands. However, in clinical operations, it was found that some lymph nodes were blocked by tumor thrombi or due to the operation of high-energy instruments during surgery. The lymph nodes cannot be stained effectively. Therefore, in some cases, the lymph nodes and the parathyroid glands are still indistinguishable, and the parathyroid glands may still be mistakenly cut during lymph node dissection. For the patient in the Test group, the first step of nano carbon tracer is to inject the tracer into the thyroid for staining. After the preliminary distinction between lymph nodes and parathyroid glands, the suspected lymph nodes but unstained tissue will be quickly detected by nano fluorescence detection. If the nanofluorescence test is positive, it means that the tissue is a parathyroid gland and needs to be preserved; if it is negative, it means that it is a lymph node and can be safely removed. The double identification method of this staining + detection confirmation further reduces the situation of parathyroid glands.

Our results showed that no significant difference was found on gender, age, preoperative Calcium, Phosphorus, Magnesium and PTH, postoperative Calcium, Phosphorus and Magnesium was found in the control and test group (all the $p > 0.05$), whereas significant difference was found on the postoperative PTH between control and test group ($p < 0.001$). Moreover, significant reduced number of parathyroid misresection was found in the test group compared to the control group ($p = 0.003$). Significant difference could be found on pre- and postoperation data of blood Calcium, Phosphorus, Magnesium and PTH in both control and test group (all the $p < 0.05$).

There are several limitations in the present study. Firstly, the relative small number of the patient could result in the bias of our conclusions. Secondly, the long-term follow-up data was not obtained from all these patients. Therefore, further study with a large number of patient and complete follow-up data should be performed in the near future. Meanwhile, the subgroup analysis should be added in the future analysis.

5. Conclusions

In conclusions, we demonstrated here that a combined nanocarbon tracer and nano-fluorescence assay can be used in thyroid surgery, which is helpful to distinguish parathyroid tissue, avoid accidental injury or missection of parathyroid gland as much as possible, and reduce the incidence of postoperative hypocalcemia.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.arabjc.2022.103709.

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