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FLUORESCENCE-IMAGE GUIDED SURGERY IN THYROID DISEASE TO PREVENT HYPOPARATHYROIDISM AND HYPOCALCEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

This review aims to explore the potency of fluorescence-image guided surgery to prevent both complications. This review was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement. Medline, Scopus, and CENTRAL databases were used to identify abstracts using predefined search terms. Two independent reviewers reviewed the abstracts and were selected according to inclusion and exclusion criteria. Risk of bias in non-randomized studies - of intervention tool was applied to reduce any potential of bias in included studies. The mean and standard deviation of 1-day after the surgery of parathyroid hormone (PTH) and serum calcium level were extracted. Any potential heterogeneity was evaluated with I2. Seven articles were included in this review. The meta-analysis showed that a total thyroidectomy with fluorescence has significantly higher PTH levels than the control group (g = 0.29; 95%CI = 0.02 – 0.57). In the subgroup analysis, ICG arm had a significant contribution for maintaining the PTH level post-operatively (g = 0.48; 95%CI = 0.24 – 0.72) while NIRAF did not (g = 0.04; 95%CI = -0.18 – 0.26). In both subgroups, the heterogeneity was negligible (I2 = 0%; P = 0.52). The analysis of serum calcium level reported that the FIGS group has a higher serum calcium level in comparison with the control group and it was significant (g = 0.48; 95%CI = 0.29 – 0.66). The heterogeneity was low and not significant (I2 = 19%; P = 0.29). FIGS has showed its usefulness for preventing two major endocrine complication following thyroidectomy.
Keywords: fluorescence; surgery; thyroidectomy; hypoparathyroidism; hypocalcemia

Introduction

Thyroid nodule is a pathological discrete lesion that radiologically distinct from the surrounding thyroid parenchyma.[1,2] This structure is built of abnormal local growth of thyroid cells and 5 – 10% of the thyroid nodule patients will develop malignant thyroid cancer.[1–3] According to Alexander and Cibas[2], thyroid nodule incidence in adult patients can be high as 50% of the total population, however, only 7 – 15% that has a clinically significant and only 2 – 6% can be detected with physical examination. Although it is scarce, thyroid nodule is more common in women than man with the global incidence of 10.1/100,000 and 3.1/100,000, respectively.[3] When the thyroid nodule has been diagnosed under a series of diagnostic approach, thyroidectomy is recommended to prevent an unwanted outcome, especially a malignant case.[1,3]

Thyroidectomy is a surgery procedure by removing the thyroid gland (TG) that is often required for treating both benign and malignant conditions.[1,3] Although it is a common and relatively safe procedure, post-operative complications such as hypoparathyroidism and hypocalcemia should be considered as a risk.[4] As the anatomical of parathyroid gland (PTG) is adjacent to TG, the PTG often gets resected or injured by accident or intentionally.[5,6] Moreover, both TG and PTG are morphologically similar which makes harder for surgeon to distinguish these structures.[7] Since the parathyroid gland secretes parathyroid hormone (PTH) that directly involves in serum calcium homeostasis, hypoparathyroidism and hypocalcemia usually follow.[2,5,6,8] Slycke *et al*.[9] reported that the rate of temporary hypoparathyroidism occurrence in a patient was 6.4 – 48.3% and permanent hypoparathyroidism was 0.6 – 14.5%. Meanwhile, temporarily hypocalcemia may occur 20 – 30% of patients and remains permanent in 1 – 4%. Both complications are life-threatening and thus impair quality of life.

Nowadays, an innovation to identification and preservation of parathyroid glands during surgery has been developed. Fluorescence is a technique that illuminates a specific structure when a specific range of light is emitted and targeted toward the structure.[10–14] This technique can help the surgeon during the thyroid or parathyroid surgery to differentiate one and the other structure, mostly between tumor and healthy tissue. Hence, it is called fluorescence-imaging guided surgery (FIGS). Commonly, there are two approaches in FIGS: contrast-enhanced fluorescence and autofluorescence imaging.[10,13] Contrast-enhanced fluorescence requires an injection of contrast agent such as fluorescent methylene blue, indocyanine green (ICG), or 5-aminolevulinic acid. The agent is subsequently absorbed by the targeted structure. When a near infrared light is directed to the parathyroid gland, the agents will absorb a specific wavelength of light and reflect the rest. [10,13] The illuminance that is emitted by the organ can be detected by a dedicated camera. Whereas autofluorescence is dye-free technique that does not any administration of fluorescence agents. [10,13] The concept behind this technique lays on an endogenous fluorophore tissue that reflects a fluorescent signal when exposed to specific wavelength of light. [9,10,13] Therefore, it is also called near infrared autofluorescence (NIRAF).

Since it gains its popularity, FIGS has been used widely. Lately, thyroid surgery has applied FIGS to differentiate TG and PTG to prevent hypoparathyroidism and hypocalcemia after the surgery. However, as it is relatively novel technique, the potential of FIGS for hypoparathyroidism and hypocalcemia prevention is still scattered. Hereby, this review aims to explore the potency of FIGS to prevent both complications. Thus, both contrast enhanced fluorescence and NIRAF were analysed further to prevent hypoparathyroidism and hypocalcemia.

Method

Data Source and Search Strategy

This systematic review and meta-analysis were conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 (PRISMA 2020) statement.[15] Using PubMed, Scopus, and CENTRAL database, searching of literature was performed using keywords listed in appendix **Table S1** on July 23th, 2023. The study must be written in English, the full text was available, and published between 2013 to 2023 to be included in this review.

Study Selection

The study selection was based on the following inclusion criteria: 1) the total thyroidectomy was performed; 2) the disease was limited to thyroid nodule only; 3) the fluorescence was compared to the control group and the control group was not limited to conventional total thyroidectomy. For better and reliable results, the following exclusion criteria were applied: 1) the article was a cross-sectional study or case report study; 2) the measurement of parathyroid hormone and serum calcium were not reported; 3) the full text article could not be received; 4) pre-post intervention analysis only.

Risk of Bias Assessment and Level of Certainty Assessment

To enhance the quality of included studies, the risk of bias in non-randomized studies - of intervention (ROBINS-I).[16] The assessment was carried out by two reviewers (FH, IP) independently. Any disagreement was resolved by consensus meeting between reviewers. The certainty of evidence was evaluated using the modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework where the quality of evidence was regarded as very low, low, moderate, and high.

Data Extraction

Author's name, year of publication, country, study design, the fluorescence, surgical method, and complications following the surgery were extracted. For the meta-analysis, the mean of serum PTH and serum calcium level and its respective standard deviation (SD) post-operative day 1 (POD 1) were obtained. If the article reported the rate of hypoparathyroidism and hypocalcemia instead of PTH and serum calcium level, under the guidance of Cochrane Handbook for Systematic Reviews of Interventions, the data was converted first into odds ratio (OR) with 95% confidence interval (95%CI). With the obtained OR and 95%CI, the OR and 95%CI must be transformed first into Ln(OR) and standard error (SE), respectively, using the formula published by Chinn[17]:

$$SE = \frac{\ln(95\%CI\ upper\ limit) - \ln(95\%CI\ lower\ limit)}{3.92}$$

After the Ln(OR) and SE were acquired, both parameters must be multiplied by $\sqrt{3}/\pi$ to Hedges' g. Hence, the forest plot can be generated since parameters have become identical.

Statistical Analysis

The random-effect model was applied since the population across studies may be slightly different. This was done by applying DerSimonian & Laird method.[18] Two-step analysis was performed. First, all continuous variables were analyzed first to get the SMD and its 95%CI. Then, with the help of Microsoft Excel 2016 (Microsoft® Office Excel® 2016, Washington, United States), the SE of respective SMD were calculated with the following formula:

$$SE = \frac{95\%CI\ upper\ limit - 95\%CI\ lower\ limit}{3.92}$$

Second, the *g* and SE from both dichotomous and continuous variables were analyses further with generic inverse variance method with *R studio ver. 4.0.0* (R Foundation for Statistical Computing, Vienna, Austria). Subsequently, a subgroup analysis (contrast enhanced fluorescence and NIRAF) was done in both PTH and serum calcium level outcomes. Heterogeneity was investigated with Cochran's Q test and I^2 statistics and the heterogeneity was classified as negligible, low, moderate, and high to I^2 value of 0%, 25%, 50%, and 75%, respectively.[19] The significance heterogeneity was considered if the *p*-value was less than 0.1. The potential of publication bias was evaluated with Funnel plot visually and Egger's test quantitatively if the included studies were more than 10 articles. The significance was set at 0.1. For the sensitivity analysis, leave-one-out method was selected. By removing one-by-one the included studies, the influence of each included studies to the pooled estimated effect can be analysed. This analysis did not intend to exclude the study.

Result

Selection of the Studies

Two hundred and thirty-nine articles were found during the searching. After the removal of duplicates, 60 articles were excluded as the article did not fulfill the inclusion criteria. No article could not be retrieved. Therefore, 179 articles were fully assessed. Under the exclusion criteria, 109 articles were removed. The remaining 70 articles were fully assessed. After full text had been assessed, 7[8,20–25] articles were included and extracted for meta-analysis synthesis since all 7 studies utilized the FIGS method in comparison toward conventional thyroidectomy and the outcome – either as primary or secondary – investigated the PTH level or serum calcium level after the surgery had been done on a day after the surgery. The flow summary of study selection is shown in **Fig. 1**.

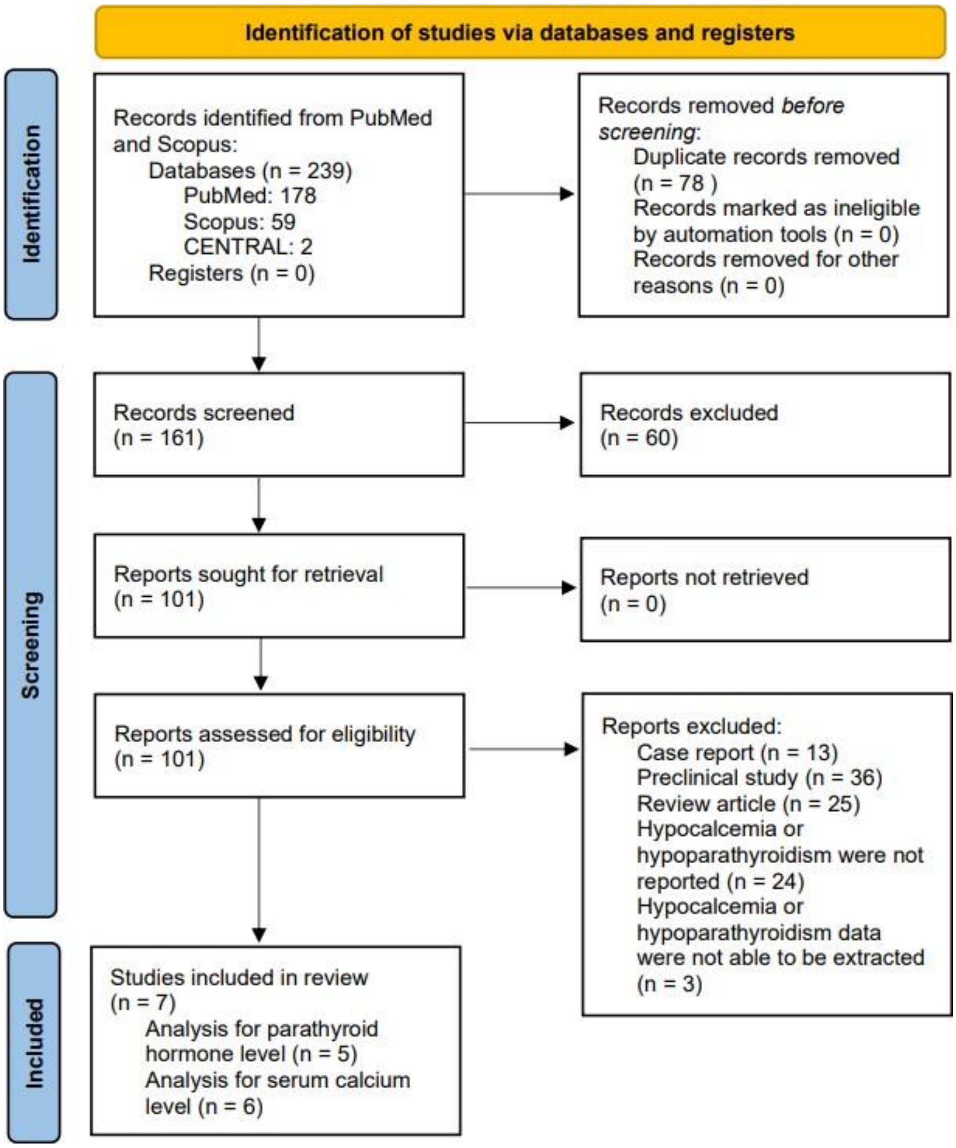

Fig 1. Flowchart of the study

Table. 1. Characteristic of the included studies.

Author, Year	Participants	Study design	Country	Thyroid disease	Surgical Approach	Fluorescence technique	Control Group intervention	Complications
Benmiloud et al., 2019[8]	241	Prospective multicenter randomized controlled trial	France	Cancer (n=38) Multinodular goiter (n=136) Toxic multinodular goiter (n=12) Grave's disease (n=53) Thyroiditis (n=1) Not determined (n=1)	Total thyroidectomy	NIRAF	Conventional thyroidectomy	Hypoparathyroid, hypocalcemia, & the rate of inadvertent PG resection
DiMarco et al., 2019[23]	269	Prospective cohort	United Kingdom	Thyroid cancer	Total thyroidectomy	NIRAF	Conventional thyroidectomy	Hypoparathyroid, hypocalcemia, & Inadvertent parathyroidectomy
Dip et al., 2019[21]	170	Randomized controlled trial	Argentina	Thyroid cancer (n=82) Goiter (n=66) Follicular adenoma (n=16) Hyperthyroidism (n=5) Hurthle cell cancer (n=1)	Total thyroidectomy	NIRAF	Conventional thyroidectomy	Hypocalcemia
Kim et al., 2020[25]	300	Retrospective cohort	United States of America	Toxic nodular goiter (n=13) Nodular goiter (n=81) Graves' disease (n=40) Malignancy-microscopic (n=92) Malignancy-macroscopic (n=74)	Total thyroidectomy	NIRAF	Conventional thyroidectomy	Hypoparathyroid, hypocalcemia, & Inadvertent parathyroidectomy
Ouyang et al., 2022[20]	81	Retrospective cohort	China	Thyroid cancer (n=81)	Total thyroidectomy	ICG	Conventional thyroidectomy	Hypoparathyroid & hypocalcemia
Yin et al., 2022[22]	180	Randomized controlled trial	China	Thyroid cancer (n=180)	Total thyroidectomy	ICG	Conventional thyroidectomy	Hypoparathyroid
Zhang et al., 2020[24]	48	Prospective cohort	China	Thyroid cancer (n=48)	Endoscopic surgery thyroid cancer via a breast approach	ICG	Carbon nanoparticle	Postoperative hoarseness and hypothyroidism

Characteristic of Studies

Seven articles were selected and included in this study with a total of 1,289 participants. Most studies conducted in China (3 articles)[20,22,24] while the rest were come from United Kingdom[23], United States of America [25], Argentina [21], and France [8]. Three studies[20,22,24] investigated the use of contrast enhanced fluorescence using ICG on thyroidectomy while the rest[8,21,23,25] observed NIRAF. The randomized controlled trial was utilized in three studies[8,21,22] while the remaining[20,23–25] was observational studies. The detailed characteristic of the included studies is shown in **Table 1**. Bias assessment revealed most studies has a low-to-moderate risk of bias. Confounding control and bias in outcome measurement were two domains that were at the high risk. Three articles failed to control the confounders and four studies did not minimize the measurement bias since the surgeon was involved directly during the surgery and data analysis. Nevertheless, since ROBINS-I is a tool specialized for non-randomized controlled trial and observational studies[16], it was expected that the risk in observational studies should be higher and none-to-low bias in randomized controlled trial. The summary of bias assessment can be seen in **Fig. 2**. Since the total of included studies were less than 10 articles, publication bias cannot be evaluated.

Parathyroid Hormone Level After the Fluorescence Image-Guided Surgery

For the meta-analysis of PTH level in POD 1, 5 articles were used with a total of 878 participants. The meta-analysis showed that a total thyroidectomy with fluorescence has significantly higher PTH levels than the control group (g = 0.29; 95%CI = 0.02 – 0.57; **Fig. 3**) which means in the FIGS group, hypoparathyroidism can be prevented. A significant moderate heterogeneity was detected (I^2 = 51%; *p-value* = 0.04). In the subgroup analysis, ICG arm had a significant contribution for maintaining the PTH level post-operatively (g = 0.48; 95%CI = 0.24 – 0.72) while NIRAF did not (g = 0.04; 95%CI = -0.18 – 0.26). In both subgroups, the heterogeneity was negligible (I^2 = 0%; *p-value* = 0.52), hence the heterogeneity can be explained by the selected technique itself. In sensitivity analysis, by removing Kim *et al*. study, the heterogeneity fell to 6% (95%CI = 0.17 – 0.65, **Fig. S1**) which concluded that Kim *et al*. study had a significant influence in this meta-analysis. Under the GRADE assessment, the level of certainty of this outcome was evaluated as high (**Table S2**).

Calcium Serum Level After the Fluorescence Image-Guided Surgery

The meta-analysis of calcium level at POD 1 after the intervention was executed with 6 articles with 1,241 participants in total. The analysis reported that the FIGS group has a higher serum calcium level in comparison with the control group and it was significant (g = 0.48; 95%CI = 0.29 – 0.66; **Fig. 4**). The heterogeneity was low and not significant (I^2 = 19%; *p-value* = 0.29). In the subgroup analysis, similar to the PTH subgroup analysis, it was revealed that ICG could maintain the serum calcium level after the surgery significantly (g = 0.60; 95%CI = 0.35 – 0.85). On the other hand, NIRAF also showed a significant impact on serum calcium level post-operatively (g = 0.41; 95%CI = 0.12 – 0.70). A non-significant low heterogeneity was detected on NIRAF subgroup exclusively (I^2 = 29%; *p-value* = 0.24). As previous analysis in the PTH group, Kim *et al* was found to have a high influence on the meta-analysis as well in this group (**Fig. S2**). The level of certainty based on GRADE assessment on hypocalcemia prevention was evaluated as high (**Table S2**).

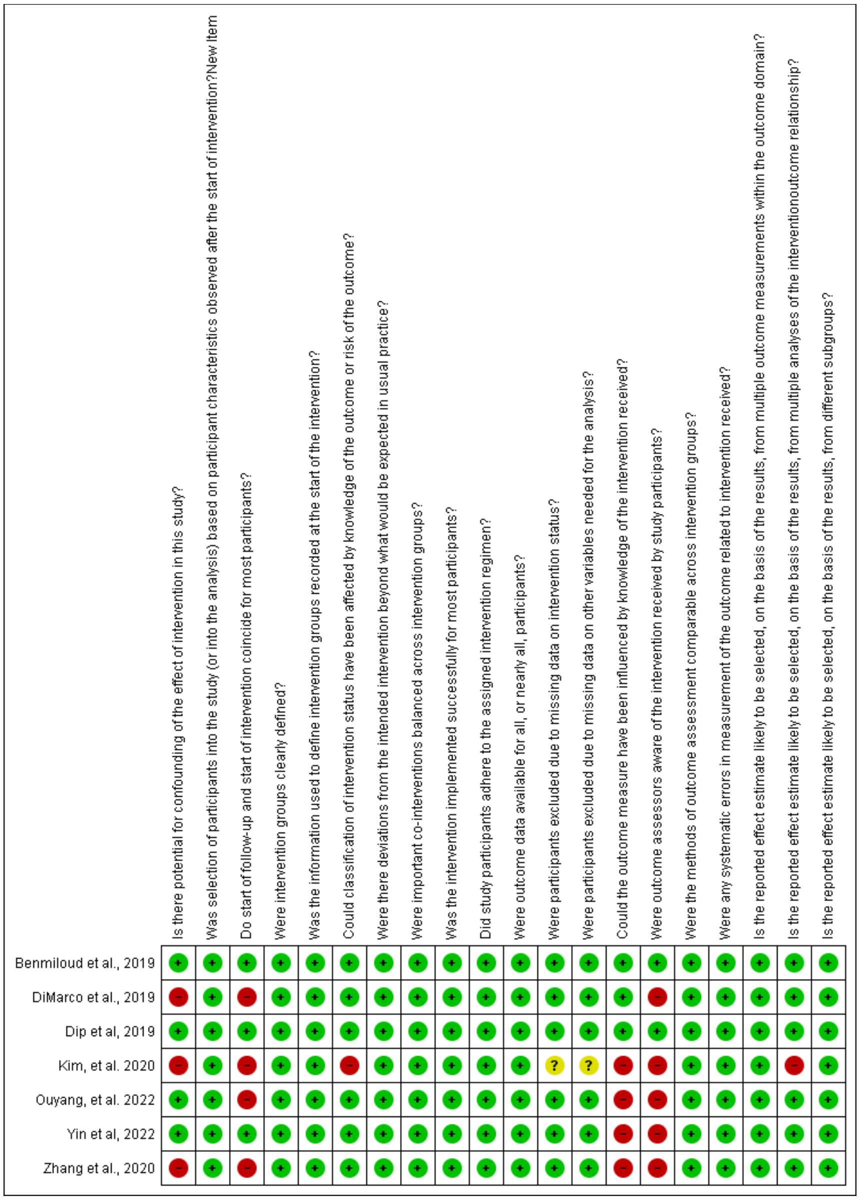

Fig. 2. Summary of bias assessment based on the risk of bias in non-randomized studies - of intervention.

Yan Wisnu Prajoko / Afr.J.Bio.Sc. 6(5) (2024). 1242-1254

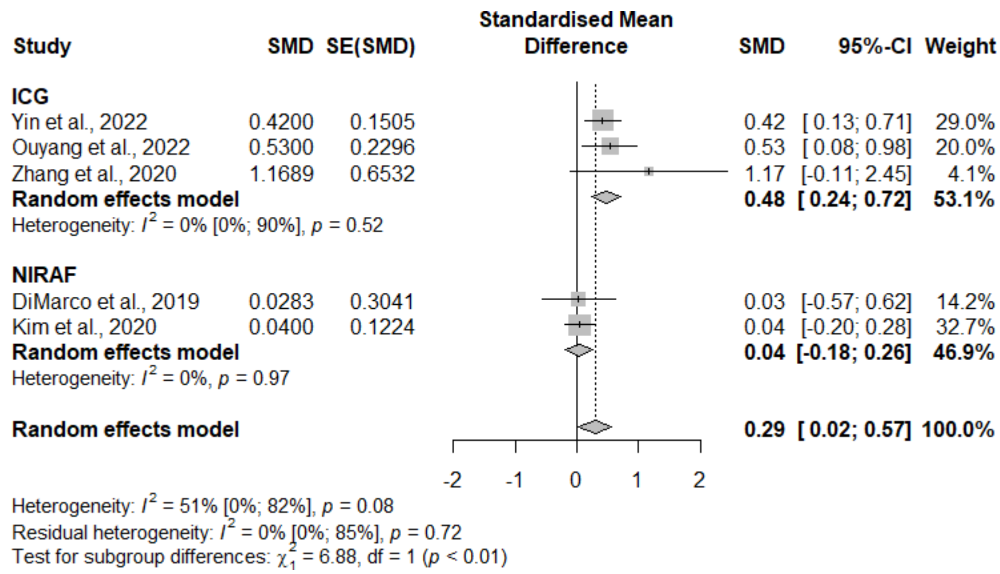

Fig. 3 The meta-analysis on parathyroid hormone level 1-day after the surgery

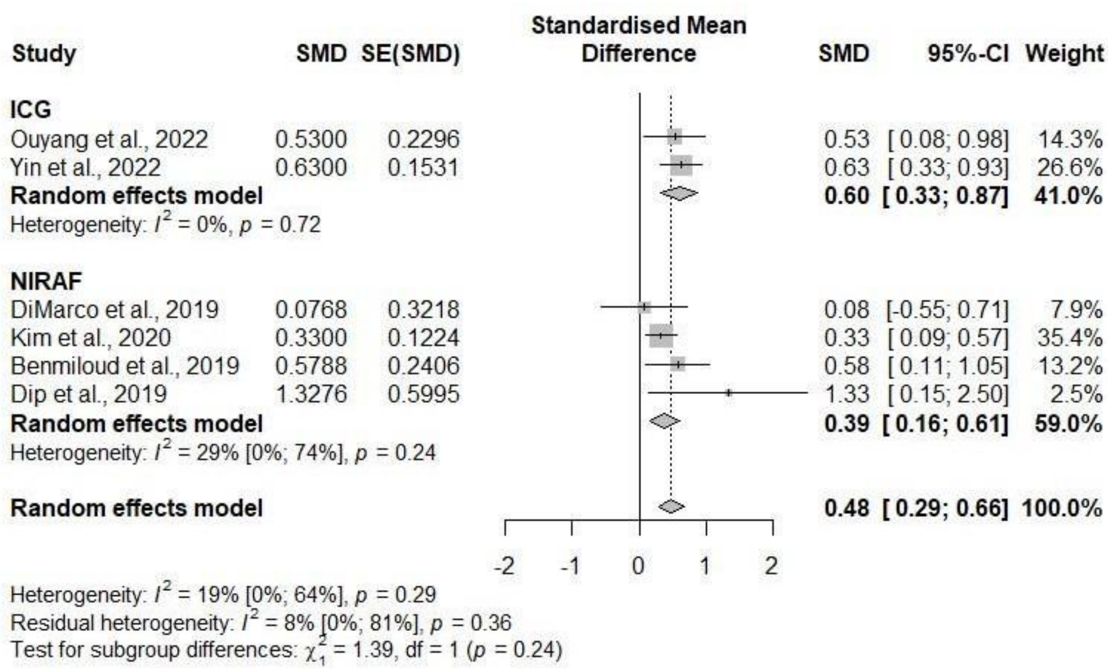

Fig. 4 The meta-analysis on serum calcium level 1-day after the surgery

Discussion

Head and neck anatomy region has been known as one of the most complex body structures. Hence, a surgery in this region must be done carefully and precisely. In thyroid surgery, aforementioned, the TG and PG are adjacent one to the other and PG is prone to be resected as well or injured during thyroidectomy which later rises major endocrine complications: hypoparathyroidism and hypocalcemia.[4,7,9,10] Although it is rare, post-thyroidectomy patients experience these downsides and complain a physical to emotional difficulties such as fatigue, muscle twitching and spams, cardiac abnormalities, coma, anxiety, depression, personality disorders, cognitive difficulties, etc.[5,6,26] Subsequently, as reported by Vokes T[6], hypoparathyroidism and hypocalcemia directly involves decreasing the health-related quality of life of the post-thyroidectomy patients.

As hypoparathyroidism and hypocalcemia are challenging, numerous approaches have been developing since then. Minimally invasive interventions have been widely accepted and used in daily practice. Thyroid ablation – a technique that locally destructs a pathological structure in the thyroid – has become popular recently.[27] This technique has a lot of variations: laser ablation (LA), radiofrequency ablation (RFA), thermal ablation (TA), microwave ablation (MA), and percutaneous ethanol ablation (EA).[27] Trimboli *et al*.[28] reported that RFA and LA has demonstrated an efficacy to reduce the thyroid nodule significantly. Ha *et al*.[29] in their network meta-analysis tried to compare the most efficacious between RFA and LA. Under their network meta-analysis, RFA turned to be the more efficacious than LA. Other meta-analysis by Chung *et al*.[30] also evaluated the safety of RFA in thyroid nodule and their findings showed that the overall complication of RFA was low as 1.35% (95% CI = 0.89%–1.81%) with vocal voice changes as the commonest complication. Nevertheless, hypoparathyroidism and hypocalcemia were not explored in these articles. Moreover, the investigation of thyroid ablation use in malignant pathology is scarce since in thyroid cancer, the removal of thyroid gland remains the first line treatment which gives a limited use of thyroid ablation use in malignancy cases.

In such case, FIGS can be used as an additional skill for the surgeon during the thyroidectomy. In the present meta-analysis, FIGS – either contrast-enhanced fluorescence and NIRAF – has demonstrated its ability to preserve PTH and serum calcium level POD 1 (g = 0.29; 95%CI = 0.02 – 0.57; g = 0.48; 95%CI = 0.29 – 0.66; respectively). However, contrast-enhanced fluorescence has given more benefit for PTH preservation and serum calcium level than NIRAF. Although the analysis is limited only a day after the surgery, it should be noted that a PTH and calcium level a day after surgery is the best predictor for permanent hypoparathyroidism and hypocalcemia.[31] In hypoparathyroidism analysis – despite its effectiveness to preserve the PTH level – the selection between contrast-enhanced fluorescence and NIRAF should be considered since both groups has a diverse effectiveness (I^2 = 51%; P = 0.08). Considering the hypoparathyroidism outcome, the subgroup analysis showed that contrast-enhanced fluorescence has a better preservation of serum PTH level (g = 0.48; 95%CI = 0.24 – 0.72) than NIRAF (g = 0.04; 95%CI = -0.18 – 0.26). This can be explained by the mechanism of contrast-enhanced fluorescence itself which requires a fluorescence contrast injected before the surgery and detected by a dedicated camera.[7,10,13] As a result, the PGs can be identified visually more precise than NIRAF.[11,12,20,22,24] This was also stated in a prior systematic review by Demarchi *et al.*[10] Moreover, contrast enhance fluorescence using ICG can evaluate the PG perfusion as well. Moreover, when all PGs can be identified, ICG has a high diagnostic accuracy, specificity and positive predictive value for detecting early hypoparathyroidism.[12] In contradiction, in hypocalcemia analysis, both techniques did reduce the postoperative hypocalcemia and the heterogeneity was low. This unique finding unfortunately cannot be explained in this review due to limited resources investigated this matter.

The present meta-analysis dedicated to investigating the use of fluorescence in thyroid surgery to prevent hypoparathyroidism and hypocalcemia. It turns out the meta-analysis demonstrates the utility of fluorescence to maintain serum PTH and serum calcium level. Despite that, this review did not analyse the pathology of thyroid nodule as benign and malignant since most of included studies were observed the fluorescence limited to thyroid cancer whilst only 2 articles included benign thyroid disease in their analysis. Moreover, the follow up of serum PTH and serum calcium level were available mostly at the day after surgery only when a transient or permanent hypoparathyroidism or hypocalcemia are only observed after a designated time. This is also the limitation of this review since the designated time for the transient or permanent endocrine complications was not standardized which halted a further analysis. Additionally, the cut-off across the included studies to diagnose hypoparathyroidism and hypocalcemia were not set due to diverse cut-off was reported while the sensitivity and specificity data were often not available. In addition, the included studies might use a different surgical approach based on the surgeon's experience which may rise some bias that was not detected by the conventional ROB tools.

Clinical Implication and Further Research

The current evidence shows the superiority of FIGS over the conventional thyroidectomy to prevent both hypocalcemia and hypoparathyroidism a day after the surgery. Regarding the technique of FIGS – contrast-enhanced fluorescence or NIRAF – there is no direct evidence yet that shows the superiority between those two. However, contrast-enhanced fluorescence currently has a superiority over the NIRAF indirectly in PTH preservation. Nonetheless, this review did not investigate the long-term effect of FIGS since the lack of evidence. Hence, it is encouraged for the future research to investigate long-term effect of FIGS to prevent the permanent hypoparathyroidism and hypocalcemia.

Conclusion

FIGS has showed its usefulness for preventing two major endocrine complication following thyroidectomy, hypoparathyroidism and hypocalcemia by precisely identifying the source of PTH – the main hormone that plays a key role on serum calcium control – the parathyroid gland. However, since contrast-enhanced fluorescence has demonstrated a better serum PTH control better than NIRAF, the approach for thyroidectomy in thyroid nodule should be considered.

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