

**Indocyanine Green Florescence Angiography for the preservation of Parathyroid Gland during Thyroidectomy - A short review and perspectives**

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**Abstract**

For endocrine surgeons worldwide, localising the parathyroid glands intraoperatively during thyroid surgery is of utmost importance. Recently, with the introduction of Indo cyanine green (ICG) fluore scence imaging techniques and its application in endocrine surgery, the identification and presser vation of para thyroid glands has become much easier. This ‘real time intraoperative technique’ involves the use of various devices with ICG as the inert contrast agent to visualise the parathyroid gland and assess its vascularity. This mini review aims to describe the present application of ICG angiography in parathyroid preservation.

**Keywords:** Indocyanine green, angiography, parathyroid glands, thyroid surgery,

**Introduction**

The parathyroid glands are usually four delicate structures of 3-4 mm in size, located in close proximity with the thyroid gland. Their essential function is main taining the calcium homeostasis by producing the para thyroid hormone (PTH). Intraoperative identification of parathyroid gland is a major concern during thyroid

surgery. Iatrogenic injury of the parathyroid gland leading to inadvertent removal, damage or devasculari zation is one of the important complications after total thyroidectomy [1]. Transient and long-term hypo para thyroidism resulting in hypo calcaemia in patients undergoing total thyroidectomy is seen in up to 20% of the cases [2, 3] and accounts for up to 60% of all com plications [4]. The resultant hypo calcaemia can result in increased morbidity, including cardiac arrhy thmias, tetany leading to prolonged Hospitalisation and even death [5]. Although visual inspection is the mainstay of para thyroid identification during surgery, several techniques have been carried out for parathyroid visuali sation, but most are of limited value or have become obsolete [6]. There is no reliable noninvasive method to identify a parathyroid gland intraoperatively. Hence, there was a need to develop tools to help the surgeon identify the parathyroid gland during surgery in an objective manner.

Dudley et al [7] first developed the technique of the use of intra venous methylene blue for rapid identification of para thyroid glands. With time, there have been advances

in the realm of medical technology. The emergence of near infrared (NIR) fluorescent imaging techniques used intra-operatively has been of interest in recent times [9]. Indo cyanine green (ICG) fluorescence and para thyroid auto fluorescence are two recent techniques developed with an aim to help with the intra operative identification of the parathyroid glands during thyroidectomy and thus safeguarding them. We write this mini review to illustrate the current perspectives of ICG Angio graphy in para thyroid preservation.

### **ICG fluorescence in Surgery**

Indocyanine green (ICG) is an inert, water soluble, amphiphilic tri carbocyanine organic dye that when delivered intra venously bind to plasma lipoproteins and confines to the intravascular compartment until it is cleared exclusively through hepatobiliary system due to first pass effect. It has a half-life of  $3.4 \pm 0.7$  min, which allows repeated applications. Once excited by near infrared wavelengths of around 800nm, the ICG will fluoresce [9]. The utility of indocyanine green was first shown in ophthalmic practice for fundus angiography [10]. Later studies were done to evaluate the feasibility and efficacy of use of ICG intraoperatively in abdominal surgeries such as identification of structures of biliary tract and bowel perfusion [11, 12] with further application in Endocrine Surgery.

### **The modern era of Thyroid Surgery**

The history of thyroid surgery starts in the second half of 19th century with Kocher, Bill Roth and Halsted, who first developed a safe technique of thyroid resection. Since then, the objectives for thyroidectomy are: conservation of the parathyroid glands and preserving laryngeal nerves, an accurate haemostasis and excellent cosmesis as described by the magnificent seven [13]

The conventional technique of parathyroid identification is by visual inspection. They typically appear ellipsoid,

pea sized and is of a reddish-brown colour making it difficult to visualize during surgery. Postoperative temporary Hypo calcemia being the most common complication after thyroid surgery warranted new techniques to be put forth to identify parathyroid gland intra operatively. Several techniques were carried out for para thyroid gland identification such as the use of methylene blue dye, ICG fluorescence imaging, intra operative frozen studies and para thyroid auto fluorescence imaging. It was Suh et al in 2014 who showed that para thyroids could be visualised using ICG NIR imaging during thyroid surgery in dogs [22]

Initial study done by Zaidi et al [8] studied the feasibility of ICG fluorescence imaging to identify parathyroid glands during surgery. The results were promising with up to 84% of the parathyroid glands exhibiting ICG fluorescence during Thyroidectomy. This potentially gave a new realm to use technology to safeguard the parathyroids and thereby prevent their inadvertent injury.

### **Hazards of Hypoparathyroidism**

Apart from hypocalcemia, causing the patient to be on long term calcium supplementation, hypo parathyroidism has a wide spectrum of deleterious effects. Long term complications included chronic kidney disease due to altered calcium homeostasis, neuro psychiatric derangements, basal ganglia calcifications and infections [18, 19]. Tackling and preventing such occurrences is the modern challenge faced by surgeons, necessitating the need to use modern technologies at our disposal for the patient's benefit.

### **Safety of Indocyanine green**

ICG contains 5% of sodium iodine and any adverse effect is attributed to the Iodide content. In a large study, the occurrence of anaphylaxis or hyper sensitivity reaction was reported to be 0.0017% (4/240000 cases), 17 adverse events in 34 years [23]. It has also been shown that intra

operative ICG administration can be a potential cause of “black thyroid” phenomenon [24] but causing no morbidity or mortality. In none of the research done to study the use of indocyanine green Fluorescence during thyroid surgery has there been an adverse event reported to ICG injection [20].

**Utility of ICG fluorescence imaging in thyroidectomy**

Owing to hypocalcemia being the most common morbid complication after thyroidectomy [14], there has been many studies and advances to safeguard the parathyroids with ICG fluorescence imaging being one of them showing promising results. It was in 2016, that Vidal et al from Switzerland first published a pilot study evaluating the utility of ICG angiography to predict hypo para thyroidism after thyroidectomy [15]. The technique was standardised by using ICG dye diluted in sterile water and injected intravenously following the specimen retrieval to grade the vascularity of the parathyroid glands. He concluded that with one well vascularized gland the risk of postoperative hypo para thyroidism is minimal.

On the contrary, Zaidi et al, attempted to extend the use of ICG enhanced fluorescence angiography to not only assess the vascularity, but also identify the gland during the peri-thyroidal dissection thereby safeguarding the gland [8]. The major causes identified leading to post operative deficiency of parathyroid hormone are inadvertent injury by the surgeon due to either mechanical or thermal trauma [14, 16]. There are many situations faced by the endocrine surgeon such as re-operations of the neck, Graves’ disease, large goiters, invasive thyroid carcinomas, where the identification of the para thyroid gland during thyroidectomy becomes an herculean task and the incidence of hypo calcemia exponentially increases [16, 17]. These are the circumstances where the use

of certain tools like the ICG fluorescence imaging can help the surgeon.

The two grading systems for parathyroid angiography used [8, 15] is tabulated in table no 1. Most studies published, depict a double ICG instilled during the time points of peri-thyroidal dissection and at the last step of assessing the parathyroid gland. During the first stage, to identify the parathyroids, the dye is injected and the glands are seen to fluoresce about 20-60 seconds later revealing their location [20]. Whereas, during the second stage, the intensity of fluorescence of the gland is seen to assess its vascularity thereby its viability.

Table 1: Grading systems of ICG Angiography of parathyroid gland

Sn.	Author	Camera system	Grading system
1	Vidal et al [15]	Laparoscopic PINPOINT camera (Novadaq, Ontario, Canada)	0 – no or poor vascularity 1 – moderate vascularity 2 – excellent vascularity
2	Zaidi et al [8]	PINPOINT video assisted NIR system (Nova daq)	0 – no ICG uptake 1 - <30% uptake 2 – 30-70% uptake 3 - >70% uptake

Recent studies published, extend this principle of parathyroid angiography to minimally invasive and remote access endoscopic thyroidectomies. Yu et al used ICG enhanced imaging technique with bilateral Axillo-breast approach robotic thyroidectomy (BABA) [21]. This study incorporated the Firefly system (NIR illuminator) integrated to the da Vinci Si robotic system, paving the way for further innovations in the field of endoscopic thyroid surgeries without compromising the safety.

**Limitations of ICG enhanced fluorescence imaging of para thyroid glands**

The incorporation of ICG enhanced para thyroid Angiography to assess the vascularity of the gland post thyroidectomy, is time consuming, involving more expenditure which is a major constraint in most countries.

Considering the application of ICG Angio graphy in various surgical techniques, its cost can be divided amongst other departments [25]. Although this technique was introduced with aim to identify and preserve the parathyroid glands, its utility is controversial in identification of the gland where the technique of autofluorescence has a better role. With many studies published, there is no consensus on the dose and timing of ICG fluorescence of the parathyroids, leading to varied observations.

### Conclusion

Current data suggests that ICG imaging of the parathyroid glands during thyroid surgery can help predict the occurrence of post operative hypo parathyroidism. It is a real time intra operative technique to assess the vascularity of the gland, aiding the surgeon in auto transplant decision making. Further trials are needed to validate ICG enhanced Angio graphy as a tool to objectively assess the gland function. With the introduction of this technique, the rate of morbid post operative hypo calcemia can be brought to a minimum.

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