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Research Article

Lessons Learned with the LiMON Method of Indocyanine Green Elimination

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Abstract

Aim: To report the lessons learned with the LiMON device, in assessing liver function of patients in research protocols.

Methods: Liver function was measured through Indocyanine Green (ICG) clearance, using the LiMON device. We performed 201 liver function analyses, using the LiMON device in 104 patients in different clinical situations: 53 patients before liver transplantation, 40 after transplantation, 10 among obese patients and one in a patient with a diagnosis of a hepatic tumor. Prior to each analysis, patients were monitored with an ICG finger clip connected to the LiMON device. We administered 0.25 mg/kg of ICG for each patient. ICG was injected soon after vein puncturing, immediately followed by 10 ml of saline solution.

Results: In 4% of all cases, the LiMON device did not detect the Indocyanine green and failed to evaluate liver function. Patient-related reasons were most often attributed to these failures, and as a result varied widely, ranging from hands with vaso-constriction as a result of low room temperature, nail polish, portal vein thrombosis in a cirrhotic patient, oxygen saturation below 95% in an obese patient, poor peripheral perfusion among patients using high vasoactive drug(s). In addition, the ICG dye presented a range of side effects, including allergic reactions, nausea, and respiratory distress in 0.99% of all cases. All adverse reactions were controlled with either steroid and/or anti-emetic drugs. Finally, the ICG overflowed to the subcutaneous tissue among some patients, although it was completely absorbed after a few days.

Conclusion: The use of LiMON device to measure hepatic function by ICG dye clearance is increasing due to its easy accessibility and non-invasiveness. Nevertheless it is imperative to know their limitations in order to deliver an optimal quality of care.

Keywords: *Indocyanine Green Clearance; Adverse Effects; Liver Function; Pulse Spectrophotometry; Liver Transplantation*

Core Message

There is no data in literature about the technical difficulties, the challenges and the best way to use the LiMON module (Pulsion Medical Systems, Munich, Germany) to measure Indocyanine green elimination.

Introduction

Indocyanine green (ICG) is an anionic, inert, non-toxic, water-soluble tri-carbocyanine dye, with an ideal absorption maximum at an "isobestic" point of haemoglobin. This point is the wavelength at which the extinction of both (oxygenated and de-oxygenated [1]) forms occur, is equal, making spectrophotometric determination of ICG independent of oxygen saturation and serum bilirubin concentration [2]. Upon intravenous administration, ICG binds completely to albumin and lipoprotein, is almost exclusively removed by the liver, and is excreted in bile without any entero-hepatic circulation. Its elimination is thus considered to be correlated with hepatic function [2-4].

ICG dye has been used in the medical field since 1956, when it was approved by the Federal Drug Administration for imaging cardiac and hepatic circulations [5]. It is used to assess liver function reserve in patients with chronically reduced hepatic function (hepatitis, cirrhosis) [6], in ophthalmic angiography [7], to measure function and cardiac output [8], as a predictor of survival in septic patients [9], for evaluation of critically ill patients [10], as a predictor of early post-operative complications after liver transplantation [11], as an outcome prediction tool in cardiac surgery [12], for tissue and vessel identification during neurovascular and oncologic surgery, and in the assessment of microvascular circulation [13,14].

ICG elimination can be expressed as half-lifetime, clearance, retention or plasma disappearance rate (ICG-PDR) [15]. There are various techniques to assess ICG elimination in-vivo, the gold standard relying on serial blood sampling after ICG injection along with spectrophotometric analysis of its concentration [16,17]. This method is, however expensive, invasive, time-consuming and may take as long as 45 minutes [11,18,19]. Non-invasive means of measuring ICG elimination using dye densitometry have been described since 1967 [20]. The advent of pulse oximetry and subsequently pulse dye densitometry, led to the development of commercially available devices for pulse spectrophotometry [21-23]. The LiMON module (Pulsion Medical Systems, Munich, Germany) is one of such devices in current use, this device being part of a multi-parameter monitor called PICCO2.

Although ICG is a harmless dye, an occasional allergic response to it has been observed after intravenous administration [24]. It should thus not be used in patients with known iodine allergy or thyreotoxicosis [2,18], since it contains iodine at a 5% concentration. To our knowledge, there is no data in the literature on the technical difficulties and the challenges in using the LiMON to measure Indocyanine green elimination.

In face of this gap in the literature, this study is aimed at reporting the lessons learned upon using this device in research protocols to assess subject liver function.

Methods

Since 2012, data was collected using the LiMON to: assess the liver function in Research Projects, evaluate the correlation between hepatic clearance of Indocyanine green and MELD in cirrhotic patients before the liver transplantation, evaluate early graft dysfunction through the plasma disappearance rate of Indocyanine green measured by pulse dye densitometry in the post-liver transplantation, and to assess the progress of hepatic functional reserve in obese patients undergoing bariatric surgery using Indocyanine green, as well as in patients with liver tumor before hepatectomy, in the Gastroenterology Department of Clinical Hospital of São Paulo University, School of Medicine. All the Projects were approved by the Ethic Committee of the Department.

According to the Projects, we had four groups of patients: before the liver transplantation, after the liver transplantation, obese patients and patients with liver tumor.

We performed 201 analyses of the liver function using the LiMON in 104 patients, which comprised of 75 men and 29 women. According to the groups, we had 53 patients before the liver transplantation, 40 patients after the liver transplantation, 10 obese patients and one patient with liver tumor. The age of the patients ranged from 27 to 72 years old, with a mean value of 54,5 years.

Technique

In the outpatient clinic, ward or in the intensive care unit, the patient was monitored with an ICG finger clip connected to the liver function monitor (LiMON) via an optical probe. The dose of ICG administered per patient, 0.25 mg/kg (25), was calculated based on the patient's weight. Soon after puncturing a vein in the patient's cubital fossa or in hand, an ICG bolus of 0.25 mg/kg was injected, followed immediately by 10 ml of saline solution. Administration was always performed after dilution of the ICG in 10 ml of accompanying solvent, in order to obtain a concentration of 2.5 mg/ml. Informal consent was obtained from all patients before taking the ICG test.

After injection, ICG was detected from fractional pulsatile changes in optical absorption. According to the prescribing information, the absorption peak of the ICG is between 790 nm and 805 nm, and the emission peak around 835 nm. When the LiMON device detected a stable signal of peak ICG concentration, it started to record the change in ICG concentration by the pulse spectrophotometry sensor on the patient's finger, and at the end of 6 - 8 minutes after ICG injection, an estimated fraction of ICG degradation at 15 minutes was reported, based on the degradation slope. The retention rate after 15 minutes (ICG R15) and the ICG-PDR are the most widely used parameters to express the elimination of the ICG, and thereby hepatic function. ICG R15 is expressed in percentage and is calculated by the formula CICG(15)/CICG(0) × 100 (CICG(t) = ICG concentration at time point t, in minutes). Normal values are under 10% [2]. ICG-PDR is expressed as a percentage change over time, and the initial concentration at time zero is 100%. Normal values for ICG-PDR are above 18%/min [15].

Due to possible interference of external lighting, we covered the patient's hand with the ICG finger clip with a sheet. We did not take the ICG test in patients allergic to seafood or products containing iodine in their formulation, nor in patients with thyrotoxicosis, following the recommendations of the prescribing information of the ICG. In cases of an allergic reaction to the ICG, we stopped the infusion of the ICG and we started to use steroid (methylprednisolone 125 mg IV, in bolus), as well as medicines to treat the symptoms (nausea, vomiting, headache) that eventually appeared.

Results

Some difficulties were encountered in the use of the LiMON method of Indocyanine green elimination: The hands of some cirrhotic patients were so cold that LiMON didn't detect the ICG, while other patients had painted nails, or nails with base coat. To solve the problem of reduced peripheral perfusion of the hand secondary to low room temperature, we used warm water-filled gloves. Patients with nail polish and those with base coat had their nails cleaned. After these procedures, the LiMON method was effective and the ICG was detectable.

One obese patient presented local allergic reactions, with hyperemia and urticaria, while another had a systemic allergic reaction with nausea, and respiratory distress. Both patients were treated with steroids, and the allergic reaction quickly improved.

Only obese patients had allergic reactions, corresponding to 7.1% of the times when the ICG test was performed in this sample. Since the administered dose of ICG was proportional to each patient's body weight, the absolute amount of the dye injected on this case was higher. As a result, after this patient we initiative a protocol where ICG was dilluted in 20 ml of saline solution, with no further adverse events of the same nature.

After liver transplantation, we noticed that the ICG overflowed to the subcutaneous tissue in one of the patients in the intensive care unit. This patient was continuously observed for the subsequent days, when we noted that the ICG was completely absorbed five days later, without any long-term adverse consequences to the patient.

In addition, the LiMON failed to detect the ICG in patients presenting the traits demonstrated under table 1.

Gender	Age	Diagnosis	Possible Etiology
Male	63	Cirrhosis HBV* and Diffuse HCC+	HCC spread over the liver and portal vein thrombosis
Male	57	Cirrhosis HBV and Portal vein thrombosis type IV	Portal vein thrombosis type IV
Male	26	Obesity	Weight 170 kg
Female	50	Obesity	Oxygen saturation less than 95%
Female	39	Primary biliary cirrhosis with portal hypertension	High vasoactive drug (norepinephrine 1.84 mcg/kg/min)
Male	19	Drug-induced toxic hepatitis (cyclophosphamide)	High vasoactive drug (norepinephrine 1.08 mcg/kg/min)
Female	38	Post heart transplantation Ischemic cholangiopathy	Poor peripheral perfusion

Table 1: *Patient characteristics of those having an adverse event.*
**HBV: Hepatitis B Virus; +HCC: Hepatocellular Carcinoma.*

Discussion

The ICG clearance test is the most commonly used liver function test in Asia [26], and is increasingly used in other parts of the world [24]. This method is however poorly used in the Americas, and even less in South America.

In cirrhosis, the hyper-dynamic circulation is characterized by increased cardiac output and heart rate, and decreased systemic vascular resistance with low arterial blood pressure [27]. The main cause of the onset of the syndrome is the systemic and visceral vasodilation, which eventually leads to abnormalities in the cardiovascular system [28]. As a result of this systemic vasodilation, there is less blood in the peripheral vascular system, causing cold extremities in cirrhotic patients. This is probably the reason why the LiMON fails to detect the ICG in some of these patients, likewise in patients with poor peripheral perfusion.

Intravenous use of ICG is associated with a low incidence of mostly transient and mild allergic reactions such as urticaria and headache [29], whereas moderate or severe reactions, such as anaphylactic shock, are rare and occur at percentages of somewhere around 0.05% [29-31]. According to the prescribing information of the ICG, other side effects such as pruritus, erythema, hypotension, tachycardia, nausea and vomiting are also described. In obese people biomarkers can be elevated, including C-reactive protein as well as IgE levels in blood serum. These results demonstrate that obesity might indeed be linked to increased sensitization [32,33]. In addition, elevated asymmetric dimethyl arginine in obese subjects competes with L-arginine, and inhibits nitric oxide synthesis by uncoupling nitric oxide synthases, which may ultimately lead to oxidative stress [34]. Furthermore, the total amount of ICG was greater in these patients, probably accounting for the allergic reactions among obese patients.

It is known that ICG can be effectively bound to melanin, owing to melanin's unique high-affinity sites for binding a large number of organic molecules, including dye-like materials. Side effects usually occur depending on the near infra-red laser irradiation, and can include erythema, edema, hypo and hyperpigmentation, blistering, superficial exfoliation and crusting [35]. To our knowledge, there is, no data in the literature about intravenously injected ICG overflowing to subcutaneous tissue. This finding however, did not lead to any long-term adverse consequences in this case series.

Specifically in relation to the liver, the ICG clearance rate depends on hepatic blood flow, hepatic dye clearance capacity and plasma volume in normal livers [17]. Removal of ICG from circulation depends on hepatic blood flow, parenchymal cell function and biliary excretion [15,36,37]. If there is thus an obstruction of the liver blood flow and/or a hepatocellular dysfunction, the hepatocytes will encounter problems in the course of the ICG uptake, which is probably the reason why the LiMON did not detect the ICG in the patient with hepatocellular carcinoma and portal vein thrombosis. This also applies to the case of ICG that was not detected in the patient with portal vein thrombosis type IV. e.g. a complete thrombosis of the portal vein and the superior mesenteric vein [38].

Acute liver failure, a rare but sudden clinical syndrome in people without pre-existing serious liver disease, results from fast and extensive hepatic necrosis and causes severe jaundice, coagulopathy, hepatic encephalopathy, and even multi-organ failure [39]. The most prominent causes include drug-induced liver injury, viral or autoimmune hepatitis, Wilson's disease, ischemia, some cases also being idiopathic [40]. It is also known that a decrease in liver's intrinsic ability to extract ICG from the circulation can be caused by global hepatocellular dysfunction, as in end-stage liver disease or during graft rejection after liver transplantation [2]. Despite this, there are some cases reported in literature describing liver function measurement by pulse dye densitometry in patients with acute liver failure [18]. In our particular case, the hepatocellular, dysfunctional, drug-induced, toxic hepatitis (Cyclophosphamide) was so severe that it blocked the liver's ICG uptake from the blood, and the LiMON thus failed to detect the uptake.

It has been previously described that LiMON works through transcutaneous pulse spectrophotometry [9] which measures the arterial ICG concentration, based on the difference in absorbance between oxyhemoglobin and ICG, with wavelengths of 905 nm and 805 nm, respectively. This is similar to the concept of pulse oximetry, where the arterial oxygen saturation represents the difference in absorbance between oxyhemoglobin and reduced hemoglobin, with wavelengths of 940 nm and 660 nm, respectively [18,21]. As absorption by

oxyhemoglobin and reduced hemoglobin is similarly low at both wavelengths, hemoglobin-oxygen saturation has no influence on measured ICG values [2]. However, in one obese patient with poor oxygen saturation, the LiMON did not detect the wave in ICG concentration. It has also been previously described that obesity is associated with restrictive respiratory impairment, diminished FEV1 (forced expiratory volume in one second), FVC (forced volume capacity), vital capacity, total lung capacity, functional residual capacity and expiratory reserve volume [41]. These changes are believed to be caused by the added mechanical load of adipose tissue, which reduces chest wall compliance, and impairs diaphragm descent. Obesity may also cause peripheral airway disease. The most likely direct mechanism of increased body mass index on reduced oxygen saturation might be increased ventilation/perfusion mismatch, with a possible contribution from decreased ventilation, and increased oxygen consumption [42].

Large doses of norepinephrine increase blood pressure via alpha-adrenergic-mediated vasoconstriction. Also, norepinephrine significantly induces vasoconstriction in many vascular beds, such as the skin and muscles [42]. The peripheral perfusion will either be impaired depending on the degree of this vasoconstriction. In addition, the accuracy of ICG elimination measurements may be decreased by technical artifacts caused by inadequate pulse contour tracing, in the case of reduced peripheral perfusion [2]. Norepinephrine in high doses may therefore lead to a poor peripheral perfusion, resulting in LiMON's inability to detect the ICG on patients' fingers.

Conclusion

The frequency of use of the ICG clearance test is increasing in clinical practice, due to non-invasive devices like LiMON, as well as to their easy accessibility. It is however necessary to know the limitations of the ICG dye and the device, in order for the test be conducted in the best possible manner and the safest conditions. Complications and side effects of ICG are few and can mostly be easily addressed.

Author Contributions

Pantanali CA, Gonzalez D Esteban and Asperti AM contributed equally to this work; D'Albuquerque LA and Andraus W designed the research.

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Informed Consent Statement

All study participants provided informed written consent prior to study enrollment.

Conflict-of-Interest Statement

There was no conflict-of-interest.

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