SUMMARY

Care should be taken for cirrhotic patients undergoing liver resection under general anaesthesia concerning perioperative hepatocellular integrity and kidney functions.[1,2]

Our aim is to compare Target controlled infusion (TCI) of propofol-fentanyl versus Desflurane (Des) based anesthesia in major liver resection for cirrhotic patients.

In a double blinded hospital based prospective randomized controlled study , 50 adult cirrhotic patients (Child A) were categorized into 2 groups (TCI group *n*=25 and Desflurane (D) group *n*=25) for anaesthesia maintenance. In TCI before induction all subjects received Fentanyl 3 μg/kg for 30 seconds and then an infusion of 2 μg/kg/h for 30 min, 1.5 μg/kg/h from 31−150 min, and 1 μg/kg/h until 30 min before skin closure and this is adjusted according to pharmacokinetics of Navigator. Propofol was administered with a syringe pump integrated with (controller and software) GE Healthcare Finland (Datex-Ohmeda, Helsinki, Finland). The Propofol venous blood target concentration (C_t) for induction of anesthesia was set at 4 μg/ml. During maintenance anesthetist was able to increase or decrease Et Des by 1% increments, or the Propofol (C_t) by 0.5 μg/ml to keep Entropy between 40-60 and maintain patients' hemodynamics.

Liver and Kidney functions tests, Urinary Microalbuminurea, Glutathione-S-transferase (GST), were assayed preoperatively (T_1), immediately postoperative (T_2) and 48 hours postoperatively (T_3). Haemodynamic, transfusion requirements, recovery, complications, intensive care unit and hospital stay together with economic cost were recorded.

Significant reduction in systemic vascular resistance (SVR) occurred with TCI versus Des (779±36 vs 836 ±8 dyn.sec.cm^{-5}, *P*=0.000), this was associated with a significant reduction in mean blood pressure and stroke volume respectively (85±3 vs 91±4 mmHg, 76±7 vs 86±4 ml, *P*=0.000). ALT and AST peaked in both groups at (T2), (Des) group was 378±80 and 407±35 U/L while, for TCI group was 467±38 and 413±39 U/L respectively, this increase was significantly less in (Des) group *P*=0.000. At (T3) both parameters dropped.There was no significant difference between groups regarding, GST, Microalbuminurea and ICU and hospital stay. Significant difference between both groups regarding Fentanyl intake,Des group was 270.00±29.86 and TCI group was 584.82±126.32 μgm . Extubation time was prolonged in TCI 15.20±2.629 min versus 9.76±1.507 min in Des, *P*=0.000. Des group was lower than TCI group in costs, 235 ±26 versus 438±57 Egyptian pounds or 33.70 ±3.836 versus 62.65±8.233 U S Dollars, *P*=0.000. respectively during the same surgical duration and with the same surgical team.

Desflurane appears a more appropriate choice than Target-controlled infusion of Propofol-Fentanyl in cirrhotic patients undergoing major hepatic resection surgery from haemodynamic stability, recovery characteristics and costs, but neither is superior to the other with respect to their effect on both liver and kidney organs.

CONCLUSION

- Desflurane is a more appropriate choice than Target-controlled infusion of Propofol-Fentanyl in cirrhotic patients undergoing major hepatic resection surgery due to its better haemodynamic stability, recovery characteristics and costs, but neither is superior to the other in respect to their effect on both liver and kidney.
- Significant haemodynamic parameters changes were associated with liver resection which can be summarized in significant increase in cardiac output and significant reduction in systemic vascular resistance.
- Transoesophageal Doppler is a reliable minimally invasive monitor, but the liver mobilization during resection of hepatic tumors requires frequent repositioning of the Doppler probe,this repeatedly affect the TED probe position and hence readings.

RECOMMENDATIONS

1. Desflurane is a more appropriate choice than TCI Propofol-Fentanyl in cirrhotic patients undergoing major hepatic resections from haemodynamic prospective.
2. Neither Desflurane nor TCI Propofol-Fentanyl is superior to the other with respect to their effects on both the liver and kidney. Both can be used safely for liver surgery in cirrhotic patients.
3. Close cardiovascular monitoring is essential during major liver resection and is highly recommended.
4. Transoesophageal Doppler (TED) can be used reliably as a monitoring tool for haemodynamic parameters during and after major surgical procedures.TED as a minimally invasive monitor is recommended in hepatic patients particularly with coagulopathy.
5. Laboratory markers of hepatic (blood glutathione-S-transferase) and renal integrity (urinary microalbumin) can be used to monitor perioperative changes during and after major surgery.
6. Maintaning general anaesthesia with Desflurane is cost effective and promotes early recovery in this category of hepatic patients, this supports it 's application during liver surgery.
7. Navigation system is a recommended tool when intravenous general anaesthesia is used.

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Effect Of Target-Controlled Infusion Of Propofol-Fentanyl Versus Desflurane On Hepatocellular Integrity In Cirrhotic Patients Undergoing Major Hepatic Resection.

تأثير التسريب الهادف لعقاري البروبوفول و الفنتانيل مقارنة باستنشاق الديسفلورين على الكفاءة الحيوية لخلايا الكبد في مرضى التليف الكبدي أثناء جراحات الاستئصال الجزئى للكبد.

Protocol of a thesis submitted
to the Faculty of Medicine
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In partial fulfillment of the
requirements of the degree of
Doctor in Anesthesia and
Surgical Intensive Care

خطة بحث مقدمة
لكلية الطب
جامعة الإسكندرية
إيفاء جزئياً
لشروط الحصول على درجة
دكتور فى التخدير
والعناية المركزة الجراحية

By

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For his experience in cardiac measurements.

وذلك لخبرته في قياسات القلب.

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طالبة بالفرقة الخامسة

كلية الطب

جامعة الاسكندرية

INTRODUCTION

Hepatocellular carcinoma (HCC) ranks fifth among the most prevalent cancers in the world and is the third most common cause of cancer related mortality.[1] It is frequently found in patients with chronic liver disease resulting from infection with hepatitis C virus (HCV).[2]

Resection is still the first choice for treatment of HCC[3] even at the intermediate or advanced stages.[4] Radical resection for intermediate-advanced HCC is indicated as follows: (1) single HCC with large or huge tumor nodule, swelling outward, clear border and a pseudo capsule. (2) multiple HCC with 3 or fewer nodules localized in one lobe or segment of the liver.[5]

The body can cope with removal of up to two-thirds of the liver and up to 70%–80% of the normal liver can be resected with functional compensation occurring within weeks of an operation.[6]

Major liver resection may result in complications due to metabolic insufficiency, hemodynamic changes and impairment of pulmonary gas exchange, which could lead to hepatic and multiorgan dysfunction.[7]

The site and volume of planned resection must be carefully assessed in the preoperative period, this, in addition to the patient's co-morbidities.[8]

During or after the operation which may require blood transfusions or a further operation, blood loss remains one of the main predictors of both perioperative morbidity and mortality after

liver resection.[9] More recent studies with larger numbers of both transfused and non-transfused patients have been able to confirm the detrimental effects of transfusion on the development of postoperative complications and perioperative death after liver resections.[9]

Target controlled infusion (TCI) devices allow the anesthetist to provide anesthesia by controlling the theoretical (predicted) concentration of the drug in the central compartment. Therefore, rapid changes in the depth of anesthesia are possible with similar ease to that achieved with inhalational anesthesia. But unlike inhalational anesthesia, where the end-tidal concentration of vapors can be monitored, on-line blood concentration monitoring is not practical at the present time.[10] Also, (TCI) of opioids and propofol were advocated to provide anaesthesia for major liver resection aiming to fasten patient recovery with minimal stay in the postoperative intensive care.[11]

On the other hand, Desflurane has been reported to be more innocent than other volatile agents. It is almost resistant to biotransformation and only 0.01% can be metabolized.[12]

After major liver resections in cirrhotic patients, also, postoperative hepatocellular integrity needed to be assessed through determination of glutathione S-transferase (GST) levels which seems to be a more specific indicator of liver injury.[13] An increase in GST concentrations may be detected before changes occur in routine liver function tests (aminotransferase activity, bilirubin concentrations) due to their lack of specificity and sensitivity.[13]

Combination of advanced, minimally invasive, hemodynamic assessment and monitoring such as trans-esophageal doppler(TED) improves the perioperative management and outcome of those high-risk surgical patients.[14]

TED is easy to use and avoids the complications associated with other monitoring devices. It takes minutes to be inserted, correct signal is easy to achieve, decisions on fluid therapy, inotropes, pressors and dilators usage is facilitated.[15]

Several studies have demonstrated that intraoperative fluid optimization guided by TED significantly improves outcomes, as evidenced by a decreased length of stay ranging from 30% to 40%.More over, reductions in the incidence of post operative nausea and vomiting, a shorter recovery time of gut function, and resumption of enteral nutrition have also been reported in the volume optimized groups. [16]

Until now, there has been no available literatures or research-based evidences regarding the effect of both anesthetic techniques on the perioperative events occurring among cirrhotic patients undergoing major hepatic resection. Also, the impact of preoperative cirrhosis and the decision whether to use (TCI) using propofol opioids or desflurane needs to be more investigated.

AIM OF THE WORK

- To compare between Target-controlled infusion of propofol-fentanyl versus desflurane based anesthesia in major liver resection in cirrhotic patients as regards subclinical hepatic injury, renal affection, hemodynamic parameters and postoperative course.

Patients And Methods:

The study will involve fifty adult cirrhotic (child A) patients going to be admitted to the National Liver Institute, Menoufiya University, undergoing major liver resection and they will be categorized into two groups, target controlled infusion group (TCI) and desflurane group (Des).

The sample size was calculated by using Epi Info software with the power of 80%, α=0.05. Randomization will be done by using the closed envelope technique.

A written informed consent will be taken from each patient. The study will be carried out after Research and Ethics Committee approval from both: Faculty of Medicine, Alexandria University and National Liver Institute, Menoufiya University, Egypt.

Exclusion criteria:

- Patients with a history of esophageal disease.
- Patients undergoing re-operation.
- Patients with a history of allergic reactions to drugs.
- Those who had undergone a recent anaesthetia (within the previous 7 days).
- Patients who bled profusely during their operation, who are haemodynamically unstable, or who need inotropic support.
- Patients with preoperative renal dysfunction.

Anaesthesia monitoring includes:

- Five leads Electrocardiography.
- Continuous invasive arterial blood pressure via radial artery (mmHg).
- Continuous central venous pressure via right internal jugular vein catheter (cmH_2O).
- Peripheral pulse oxymetry (%).
- Capnography to monitor end tidal (ET) CO_2(mmHg).
- Fraction inspired oxygen concentration (%).
- Urine output (ml/hour).
- Neuromuscular blockade (Train of four).
- Oesophageal temperature(degree centigrade).
- Entropy to monitor depth of anaesthesia.

(Anaesthesia Workstation, General Electric, Helsinki, Finland) -Trans-esophageal Doppler (cardioQ) haemodynamic monitoring. (Deltex Medical, Chichester, UK).

Anaesthetic technique:

A 20 gauge intravenous cannula will be inserted in the non dominant hand and used for induction of anaesthesia. Afterwards, at least two large peripheral venous lines (16 gauge or larger), multi-lumen central venous catheter in the right internal jugular vein and an arterial catheter also in the non dominant hand (radial artery will be used after doing Allen test) will be inserted.

In group Des general anesthesia will be induced with fentanyl in a dose of (1microgram/kg), propofol (2 mg/kg) and rocuronium (1 mg/kg). End-tidal desflurane concentrations during the induction will be limited to 1 MAC. Endotracheal intubation will be done after complete muscle relaxation is confirmed by nerve stimulator and anesthesia will be maintained with a mixture of air, oxygen and Desflurane at a fresh gas flow of 1 litre/min. Ventilation will be controlled to maintain $ETCO_2$ between 32 and 36 mmHg (Anaesthesia Workstation, General Electric, Helsinki, Finland).

In group TCI immediately before induction of anesthesia with propofol, all subjects will receive fentanyl 3 µg/kg for 30 seconds and will be followed by a continuous infusion of fentanyl 2 µg/kg/h for 30 min, 1.5 µg/kg/h from 31–150 min, and 1 µg/kg/h until 30 min before skin closure[10]. Propofol will be administered with a syringe pump integrated with (controller and software) GE Healthcare Finland (Datex-Ohmeda, Helsinki, Finland). The propofol venous blood target concentration (C_t). for induction of anesthesia was set at 4 µg/ml for the younger patients(less than fifty years) and 3 µg/ml for the elderly (more than fifty years).[11] If anesthesia was not induced within 5 min, the C_t will be increased sufficiently to complete the induction of anesthesia. When consciousness will be lost, rocuronium 1mg/kg, will be given and trachea will be intubated.

During maintenance of anesthesia, the anesthetist will be able to increase or decrease end tidal desflurane concentration by 1% increments in (group Des), or the propofol (C_t). by 0.5 µg/ml

in (group TCI) at any time according to entropy and patients hemodynamics.

In both groups, Entropy will be kept between 40-60. If MAP or HR remained increased after 5 min supplemental dose of fentanyl (0.5 µg/ kg) will be given. Atropine 0.5 mg will be given intravenously if heart rate drops below 45 beats/min. Anesthetics will be decreased also in response to hypotension not responsive to replacement of intraoperative fluid loss or treatment of bradycardia. Additional rocuronium will be administrated as appropriate in bolus doses and guided by nerve stimulator.

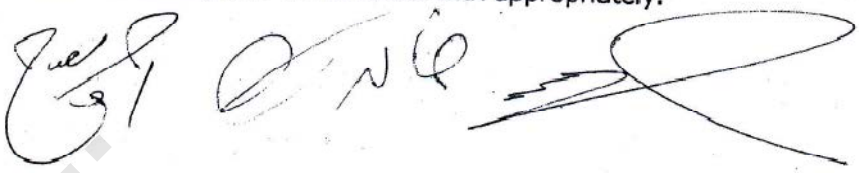
Intravenous crystalloids in the form of Ringer's acetate will be infused at a rate of 6 ml/kg/hr to replace fluid deficit and basal fluid requirements. Packed RBCs are administered to keep haematocrit more than 25%. Blood products are given, if at all, guided by the coagulation laboratory intraoperative findings. Urine output will be maintained at least 1 mL/kg/hour. Rapid infusion device is available for emergency use. Intra-operative normothermia will be maintained using a forced air-warming blanket (Bair Hugger; Arizant, United Kingdom), in addition to a warm intravenous fluid device.

Prophylaxis against deep venous thrombosis includes the use of elastic stockings and a sequential compression device for both lower limbs until early ambulation. Daily administration of subcutaneous low molecular weight heparin from the first postoperative day is practiced.

All patients are planned to be extubated on table at the end of surgery unless decided otherwise according to the

operative circumstances. At the end of surgery (whether extubated or not), all patients of both groups will be transferred to the intensive care unit (ICU).

Postoperative complications including bleeding, sepsis, nausea, vomiting, chest infection, and renal dysfunction will be monitored closely and will be dealt with appropriately.



MEASUREMENTS

1) Haemodynamic parameters will be monitored continuously and recorded before induction (t_0),immediately after induction before intubation (t_1), , 15 min after the intubation (t_2), during dissection (t_3), during hepatic resection (t_4), and near the end of surgery (t_5).

- Heart rate (beat/min).
- Mean arterial blood pressure (mmHg).
- Central venous pressure(cmH_2O).
- (CO) cardiac output (L/min).
- (SV) stroke volume (ml)
- (SVR) systemic vascular resistance ($dyn.sec.cm^{-5}$).
- (FTc) corrected flow time (msec).

2) Laboratory investigations :

a) Liver function tests will include:

-AST& ALT(U/L), total bilirubin(mg/dl), albumin(gm/dl), Prothrombin(%).

-Glutathion S transferase (GST), (IU/ml).

b) Kidney functions tests will include serum urea & creatinine(mg/dl) and microalbumin in urine(µgm/ml).

C) Metabolic parameters & electrolytes will include:

-Arterial blood gases.

-Serum electrolytes as sodium& potassium(meq/l).

Samples of GST will be kept at room temperature for almost one hour, then serum will be separated by centrifugation

for five minutes at 3000 r/min and 1ml aliquots will be frozen at -80 degree centigrade until analysis.

All laboratory samples will be collected preoperatively, immediately postoperative and 48 hours postoperatively.

3) Fluid balance (intake and output),intraoperatively and 24 hours postoperatively.

4) Time from discontinuation of inhalational agent until the trachea is extubated is recorded.

5) Modified Aldrete Scoring system for recovery score. [17]

6) Postoperative course will be assessed as follow:

a) The amount of transfused blood and blood products (fresh frozen plasma and/or platelets) in ml needed intraoperatively and during first 48 hours postoperatively.

b) Postoperative complications will be recorded .

c) Duration of ICU and hospital stay will be recorded.

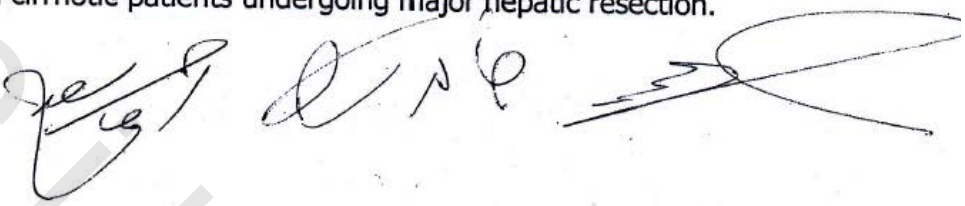
7) The total amount of inhalational agent in (ml)used intraoperatively will be calculated automatically by using the Aisys® GE Healthcare Finland (Datex-Ohmeda, Helsinki, Finland) anaesthesia machine and then will be recorded. Also, the amount of propofol(ml) used in TCI group and the anesthetic cost(LE) in both groups according to the current international prices will be recorded.

Analysis Of The Results

The data will be recorded by both manual and automatic charting and most operative data will be recorded in computerized files. Data will be subjected for statistical analysis by appropriate statistical tests using the SPSS (software package for windows), and *P* value of <0.05 will be considered to be statistically significant.

Discussion

The results are going to be discussed, with reference to the previous literatures, in the aim of identifying the effects of target-controlled infusion of propofol-fentanyl versus desflurane on hepatocellular integrity in cirrhotic patients undergoing major hepatic resection.



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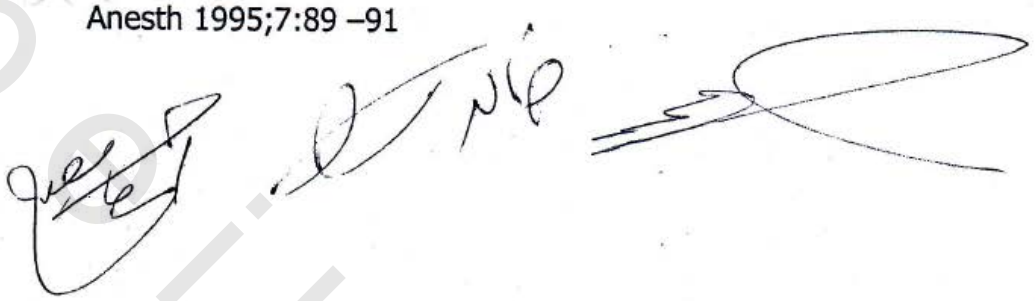

الملخص العربي

المرجعيه الدراسيه:

انه من الواجب توخي الحذر عند اعطاء المرضي المصابون بتليف الكبد تخدير كلي عند استئصال جزء من الكبد للمحافظه علي وظائف الكبد و الكلي.

الهدف من البحث:

المقارنه بين التسريب بالتحكم المستهدف لعقاري البروبوفول و الفنتانيل (TCI) مقابل عقار الدسفلورين (Des) الاستنشاقي في الاستئصال الجزئي للكبد في مرضي التليف الكبدي.

طريقه البحث:

بعد موافقه لجنه الاخلاقيات تم تقسيم خمسون مريضا مصابون بتليف الكبدتصنيف تشيلد الف الي مجموعتين :مجموعه TCI ومجموعه Des كل مجموعه خمسه و عشرون مريضا.

في مجموعة TCI قبل البدء في عملية التخدير جميع المرضي تم اعطائهم عقار الفينتانيل ثلاثه ميكرجرام /كجم لمده ثلاثون ثانيه و اعقبه تسريب مستمر للفنتانيل اثنان ميكرجرام /كجم/ساعه لمده ثلاثون دقيقة و واحد و نصف ميكرجرام /كجم/ساعه من بعد ثلاثون دقيقه حتي مائه و خمسون دقيقه ثم واحد ميكرجرام /كجم/ساعه حتي ثلاثون دقيقه قبل اغلاق الجلد.وتم حقن عقار البروبوفول عن طريق مضخه الحقن المتاكمله مع وحده تحكم البرمجيات و قد كان التركيز

المستهدف للبروبوفول في الدم اربعه ميكروجرام /لتر بالنسبه للمرضي الاصغر سنا و ثلاثه ميكروجرام /لتر للمسنين.اثناء استمرار التخدير طبيب التخدير كان قادرا علي زياده او نقصان عقار البروبوفول نصف ميكروجرام /لتر في مجموعه TCI و تركيزالدسفلوران بنسبه واحد % في اي وقت وفقا لانتروبي المرضي بين اربعون الي ستون.

تم فحص وظائف الكبد و الكلي في الدم و نسبه الميكروالبومين في البول و نسبه انزيم الجلوتاثايون اس ترانسفريز قبل العمليه و مباشره بعد العمليه و ثمانيه و اربعون ساعه بعد العمليه.

تم قياس العلامات القياسيه وكميه الدم و البلازم المنقوله للمريض كذلك دلائل الافاقه و الاعراض الجانبيه و مكوث المريض في العنايه المركزه او المستشفيو كذلك الوقت حتي اخراج انبوبه الحنجره وكذلك التكلفه الاقتصاديه.

النتائج:

حدث انخفاض ملحوظ في مقاومه الاجهزه الوعائيه في مجموعهTCI مقارنه بمجموعه Des (36vs±779) dyn.sec.cm^{-5} ±8 836, P=0.000)علي التوالي وذلك بالتزامن مع الهبوط الملحوظ في ضغط الدم و الدم المتدفق من القلب (3±85 مقابل 4±91)mmhg.و7±76مقابل 4±86)ملل. حيث P<0.01 علي التوالي.

بمقارنه وظائف الكبد وجد ارتفاع ملحوظ في قيمه كل من ALT&AST في المجموعتان مباشره بعد العمليه حيث كان في مجموعهDes كان (80±378مقابل35±407)U/L وفي مجموعةTCI(38±٤٦٧مقابل39± 413)U/L علي التوالي.و قد حدث هبوط في المجموعتان ثمانيه و اربعون ساعه بعد العمليه.ولايوجد اي اختلاف ملحوظ في المجموعتان من حيث نسبه انزيم الجلوتاثايون اس ترانسفريز و نسبه الميكروالبومين في البول وكذلك مكوث المريض فب العنايه المركزه او المستشفي.

الوقت حتي اخراج انبوبه الحنجره كان اطول في مجموعه TCI 2.629±15.2) دقيقه مقابل (1.507±9.76) دقيقه في مجموعه Des حيث P=0.000.ومن حيث التكلفه الاقتصاديه كانت تكلفه مجموعه Des اقل من مجموعهTCI حيث كان (26±235) مقابل) مقابل(57±٤٣٨)جنيها مصريا وكان (3.8 ±٣٣.٧) مقابل(8.233±62.65) دولار امريكي حيث$P=0.000$.

الاستنتاج:

عقار الدسفلوران الاستنشاقي اختيار اصلح عن عقاري البروبوفول و الفنتانيل بالتسريب بالتحكم المستهدف في المرضي المصابون بتليف الكبد عند الاستئصال الجزئي للكبد من حيث استقرار العلامات الديناميكيه و دلائل الفوقان و كذلك من حيث التكلفه الاقتصاديه ولكنهما متماثلين من حيث التاثير علي وظائف الكبد و الكلي.

تأثير التسريب الهادف لعقاري البروبوفول و الفنتانيل مقارنة باستنشاق الديسفلورين على الكفاءة الحيوية لخلايا الكبد في مرضى التليف الكبدي أثناء جراحات الاستئصال الجزئى للكبد

رسالة علمية

مقدمة لكلية الطب – جامعة الإسكندرية
إيفاءاً جزئياً لشروط للحصول على درجة

الدكتوراه فى التخدير و العناية المركزة الجراحية

مقدمة من

عمرو فاروق إسماعيل الصفتي

بكالوريوس الطب والجراحة – الإسكندرية

ماجستير التخدير و العناية المركزة الجراحية

كلية الطب
جامعة الإسكندرية
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