

REFERENCES

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PROTOCOL

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محمدة

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**EFFECT OF TWO DIFFERENT DOSES OF PREOPERATIVE
PREGABALIN ON POSTOPERATIVE PAIN AFTER
LAPAROSCOPIC GYNECOLOGICAL SURGERIES**

تأثير جرعتين مختلفتين من عقار بريجابالين قبل العملية على الألم ما بعد عمليات امراض
النساء بالمنظار

Protocol of a thesis submitted
to the Faculty of Medicine,
University of Alexandria
In partial fulfillment of the
requirements of the degree of
**Master of Anaesthesia
and Surgical Intensive Care**

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

By

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مدرس التخدير والعناية المركزة الجراحية

كلية الطب
جامعة الإسكندرية

For his experience in anaesthesia for
laproscopic gynecological surgeries.

وذلك لخبراته في تخدير منظار امراض النساء

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طبيب إمتياز

كلية الطب

جامعة الإسكندرية



INTRODUCTION

Pain is thought to be inadequately treated in one-half of all surgical procedures. Recent advances in the pathophysiology of pain have suggested that it is possible to prevent or attenuate the central neural hyperexcitability that contributes to enhanced postoperative pain.⁽¹⁾

High-quality pain control after day-case surgery is still a major challenge.⁽²⁾ Although opioids continue to have an important role in postoperative pain management, they have many side-effects.⁽³⁾ A multimodal approach has been suggested to improve postoperative analgesia and to reduce the opioid-related side-effects.⁽⁴⁾

Gynecological laparoscopy is a commonly performed procedure. Providing anesthesia for this can present a challenge, particularly in the day surgery population. Poor analgesia, nausea, and vomiting can cause distress to the patient and increased cost for the health system, because of overnight admission.⁽⁵⁾ Pregabalin and its developmental predecessor gabapentin were originally developed as spasmolytic agents and adjuncts for the management of generalized or partial epileptic seizures resistant to conventional therapies.⁽⁵⁾

Pregabalin and gabapentin are structural analogues of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), but they are not functionally related to it.⁽⁶⁾ The pharmacological basis of which is presynaptic binding to the α -2- δ subunit of voltage-dependent calcium channels that are widely distributed in the spinal cord and brain. By altering calcium currents, pregabalin reduces or modulates the release of several excitatory neurotransmitters, including glutamate, norepinephrine, substance P, and calcitonin gene-related peptide, producing inhibitory modulation of "overexcited" neurons and returning them to a "normal" state.⁽⁷⁾

The pharmacokinetics of pregabalin has proved to be linear with low variability. It is rapidly absorbed orally with more than 90% bioavailability, achieves peak plasma levels within 30 minutes to 2 hours, and shows linear pharmacokinetics with low intersubject variability.⁽⁸⁾ The side effect profile is good, with the most common adverse events being dizziness and somnolence and pregabalin has no effect on arterial blood pressure or heart rate.⁽⁹⁾

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AIM OF THE WORK

The aim of the work is to evaluate the effect of two different doses of pregabalin on post operative pain and analgesic consumption in patients undergoing laparoscopic gynecological surgeries.



Handwritten signature and date: 11/11/20

PATIENTS

After approval of Ethical Committee of Faculty of Medicine and having written informed consent from patients, the present study will be carried out in Alexandria University Shatby Hospital on forty-five female patients belonging to ASA physical status I and II aged 30-60 years old scheduled for elective laparoscopic gynecological surgeries under general anaesthesia in a prospective, randomized, double blind study using closed envelope method and placebo controlled trial.

The sample size was determined by the biostatistics department of the High Institute of Public Health using program G power.

Exclusion criteria:

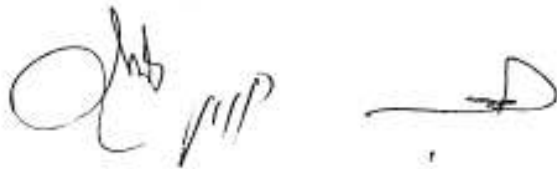
1. Impaired kidney or liver functions.
2. History of drug or alcohol abuse.
3. History of chronic pain or daily intake of analgesics.
4. Uncontrolled medical disease (diabetes mellitus and hypertension).
5. History of intake of non-steroidal anti-inflammatory drugs within 24 h before surgery.
6. Any procedure takes more than two hours will be excluded from the study.

Patients will be randomly categorized into three equal groups (fifteen patients each):

Group I: Patients will receive pregabalin 75 mg orally, hour before induction of anaesthesia with sips of water.

Group II: Patients will receive pregabalin 150 mg orally, hour before induction of anaesthesia with sips of water.

Group III: Patients will receive a matching placebo orally, hour before induction of anaesthesia with sips of water.

Two handwritten signatures in black ink. The first signature is a cursive 'Jb' followed by 'P'. The second signature is a cursive 'D'.

METHODS

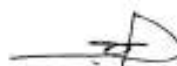
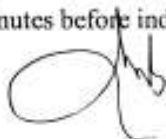
Preoperative evaluation, preparation and premedication:

Evaluation of the patients will be carried out through:

1. Proper history taking and clinical examination, to exclude cardiovascular, respiratory, neurological and metabolic diseases.
2. Routine laboratory investigations include:
 - Complete blood count (CBC).
 - Haemostatic profile study:
 - Bleeding time.
 - Clotting time.
 - Prothrombin time (PT).
 - Partial thromboplastin time (P'IT).
 - Prothrombin activity.
 - Blood urea and serum creatinine.
 - Fasting blood glucose.
 - Liver enzymes (ALT, AST).
 - Urine analysis.
3. Electrocardiography for patients above 40 years old.

Anaesthetic technique:

- Each patient will receive a matching placebo (Vitamin C) or 75 or 150mg pregabalin. All medications will be provided by hospital pharmacy, will be identical, and will be administered orally, in the ward hour before induction of anaesthesia with sips of water handled by a staff nurse who is not involved in the study.
- A 20-gauge cannula will be inserted in the ward.
- Each patient will receive intravenous midazolam 0.02 mg/kg in the ward 15 minutes before induction of anaesthesia.



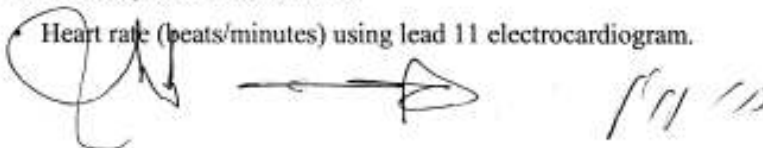
- In the theatre each patient will receive intravenous fluids in the form of lactated Ringer's solution according to the 4-2-1 rule (ml/kg/hr), during the surgery.
- Each patient will be attached to a multi-channel monitor (Trakmon, Kontron limited - England) to display:
 - Continuous ECG monitoring(lead II) for detection of dysrhythmias.
 - Heart rate (beats/min).
 - Non-invasive arterial blood pressure (mmHg) monitoring: mean arterial blood pressure (MAP), systolic arterial blood pressure (SAP) and diastolic arterial blood pressure (DAP).
 - Arterial oxygen saturation% (SpO₂).
- Anaesthesia technique will be standardized in all groups. Patients will be induced with fentanyl 2µg/kg and propofol 2-3 mg/kg.
- Orotracheal intubation will be facilitated by cisatracurium 0.2 mg/kg.
- Anaesthesia will be maintained with isoflurane 1-1.5% in 100% oxygen and maintenance dose of cisatracurium 0.02 mg/kg every 30 min guided by nerve stimulator until the end of the operation.
- At the end of surgery, residual neuromuscular paralysis will be reversed with neostigmine 0.04 mg/kg and atropine 0.015 mg/kg.
- After fulfilling criteria of extubation (regain consciousness, haemodynamically stable, regular spontaneous breathing, good muscle power) patients will be extubated and will be fast-tracked to the ward to according to the modified Aldrete score⁽¹⁰⁾, when their score will be ≥ 9 .
- In the ward, patients will receive intravenous of ketorolac with dose not exceed 30 mg/ 6h when the VAS score is more than or equal 4.

Measurements

The following parameters will be measured:

A. Hemodynamic Parameters

- Heart rate (beats/minutes) using lead II electrocardiogram.



- Mean arterial blood pressure: (MABP) will be measured in mmHg.
- Arterial oxygen saturation (SpO_2): using pulse oximeter if there is any changes.

These will be monitored continuously and recorded at the following times:

- Before induction.
- After induction.
- Every 15 minutes intraoperative.
- After endotracheal extubation.
- Postoperative every 6 hours for 24 hour .

B. Postoperative pain

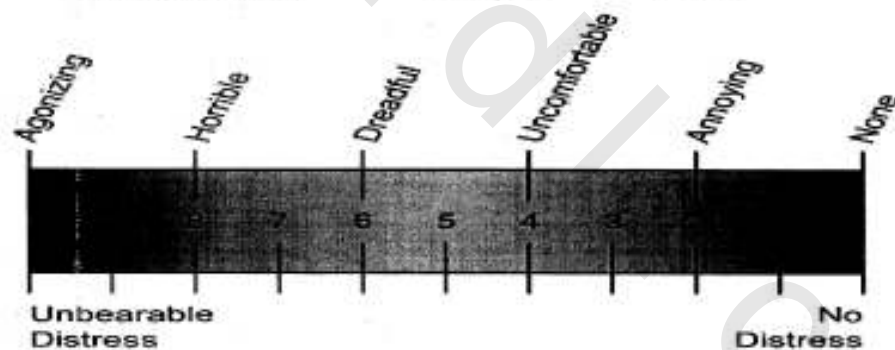
(1) Assessment of pain both at rest (static) and during coughing (dynamic).

It will be assessed using visual analogue scale (VAS).⁽¹¹⁾

Patients will be instructed the day before operation about how to use the (VAS).

Pain will be assessed on a linear scale (a 10 cm graded horizontal line):

- | | | |
|----------------------|------------|-------------|
| i. Right hand margin | No pain | score zero. |
| ii. Left hand margin | worst pain | score 10. |



Task _____

Date _____ Start _____ End _____

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Assessment of pain will be done

- 1- On arrival of patient to the ward.
 - 2- Then every 30 minutes in the first two hours.
 - 3- Then every one hour till six hours
 - 4- Then every 6 hours for the rest of 24 hours.
- (2) When postoperative pain is VAS 4, patients will receive intravenous ketrolac with dose not exceed 30 mg/ 6hour and the total administered dose in 24 hour and requirement time will be recorded.

C. Analgesic consumption

It will be assessed as follows:

1. First dose required.
2. Total requirement in 24 hours.

D. Level of sedation

It will be assessed with the Ramsay sedation score ⁽¹²⁾ as follows:

1. Patient is anxious and agitated or restless, or both.
2. Patient is cooperative, oriented, and tranquil.
3. Patients respond to commands only.
4. Patient exhibits brisk response to light glabellar tap or loud auditory stimulus.
5. Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus.
6. Patient exhibits no response.

Patients with a sedation scale of 4 will be considered as sedated.

Assessment of sedation will be done

- 1- on arrival of patient to the ward.
- 2- Then every 6 h till the end of the study, that is, 24 h after operation.

E. Postoperative nausea and vomiting

The severity of PONV will be graded on a four-point ordinal scale (0, no nausea or vomiting; 1, mild nausea; 2, moderate nausea; and 3, severe nausea

with vomiting). Rescue antiemetic ondansetron 4 mg intravenous will be given to all patients with PONV of grade 2.

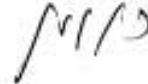
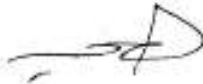
F. Postoperative side effects

Patients will be observed for any side effects during the first 24 postoperative hours in the ward such as skin rash, tinnitus, itching or others.



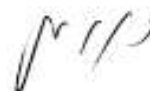
RESULTS

The results obtained from this study will be tabulated and statistically analyzed using the standard statistical methods.



DISCUSSION

The results obtained from this study will be discussed in view of achievement of the aim and compared with any available published data in the same field of the research.



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Appendix 1



Medical Research Institute
Department of Medical Statistics
Sample Size Calculation

Dr. Asmaa Abdelwahab

Sample Size Calculation Comparing 3 means

Sample Size Calculation

The minimum sample size required in each group is	Total
11	33

Summary Statements

A sample size of 11,11,11 (total 33) produces a power 90% to detect difference of mean time needed till first dose of analgesia between control (1 ± 1.25 h), group taking 75 mg pregabalin (1 ± 1.25 h) and group taking 150 mg pregabalin (3 ± 1.25 h), at level of significance of .05, using One Way ANOVA test.

References:

The sample size was calculated using
PASS 12 Program 2013 version 12.0.2.

ETHICS OF RESEARCH

Research on human or human products:

- ☒ Prospective study: Informed consent will be taken from patients. In case of incompetent patients the informed consent will be taken from the guardians.
- ☐ Retrospective study: Confidentiality of records will be considered
- ☐ DNA / genomic material: Informed consent for DNA / genomic test and for research will be taken from patients. No further tests will be carried out except with further approval of committee and patients. If the samples will travel outside Egypt the researcher will be responsible for transportation and security approval.
- ☒ All drugs used in the research are approved by the Egyptian Ministry of Health

Research on animal:

- ☐ The animal species are appropriate for the test.
- ☐ After test, if the animal will suffer, it will be euthanized and properly disposed.
- ☐ After operation, it will have a proper postoperative care.

د. محمد عبد الله
-

جاء ب

د. محمد عبد الله

11/11/11

ARABIC SUMMARY

الملخص العربي

منذ بداية استخدام المنظار في عمليات جراحة أمراض النساء بدلا من استئصالها جراحيا بالطريقة التقليدية، فقد صاحب ذلك انخفاض في حدة الشعور بالألم ما بعد العملية ولكن بالرغم من ذلك ما زال الألم يصل الي مرحلة الذروة خلال الفترة المبكرة ما بعد العملية. نتيجة لذلك فان هذا الألم هو السبب الرئيسي لبقاء المريض بالمستشفى لمدة يوم كامل وكذا طول فترة النقاهة في حالات عمليات اليوم الواحد

وبالرغم من أن للمواد الأفيونية تأثيرها الفعال للقضاء على هذا الألم، إلا أن أستخدمها يصاحبه في نفس الوقت حالة من السكون و الغثيان والقيء والتي تحدث إما بسبب إثارة الأمعاء والأحشاء أثناء العملية او كعرض جانبي للمواد الأفيونية والتي تضاف الى أسباب بقاء المريض بالمستشفى. لذا كان التحكم في الألم ما بعد العملية، ليس فقط لتقليل شدة الألم ولكن ايضا لتسريع فترة النقاهة وسرعة خروج المريض من المستشفى، هو الهدف الرئيسي لاختبار العديد من العقاقير ذات القدرة على تسكين الأم ما بعد الجراحة في الفترة الأخيرة ومن ثم كان البحث عن عقار قادر على تقليل هذا الألم وفي نفس الوقت أمن من العوارض الجانبية الشديدة وايضا عوارض التوقف التي تحدث مع استخدام المواد الإفيونية هو الشغل الشاغل للدارسين في هذا المجال للوصول الى درجة عالية من النجاح في عمليات اليوم الواحد.

كان من بين هذه العقاقير عقار البريجابالين وهو مشتق من الناقل العصبي المثبط جابا لكنه على الرغم من ذلك لا يتحد مع مستقبلات جابا أ أو جابا ب و لا حتى مستقبلات البنزوديازيبين، كما إنه لا يتحول الي جابا ولا يؤثر على عملية امتصاصه ولا تكسيره. إن عقار البريجابالين انشئ أصلا كمزيل للتشنج. كما أن فائدته كمزيل للقلق ومحور للنوم قد أدى إلى استخدامه كعقار معاون لعلاج نوبات الصرع المعمم أو الجزئي المقاومة للعلاجات التقليدية. وعلاوة على ذلك تم توسيع استخداماته العلاجية مع مرور الوقت للسيطرة على الآلام المزمنة وكذلك بعض حالات الآلام الحادة. وهو دواء سهل الإستعمال وأمن و آثاره الجانبية محدودة ، وأكثرها شيوعاً الدوخة والنعاس.

لذا كان الهدف من هذه الدراسة كان الهدف من البحث مقارنة بين تأثير جرعتين مختلفتين من عقار بريجابالين قبل العملية على آلام ما بعد عمليات امراض النساء بالمنظار.

وشملت هذه الدراسة ٤٥ مريضة في تمام الصحة من الإناث في سن ٣٠ الى ٦٠ عاما وتكون بالوضع الصحي الأول أو الثاني حسب تصنيف الجمعية الأمريكية للتخدير والتي تم اعدادهن لعمليات النساء بالمنظار الاختيارية تحت التخدير الكلي بوحدة امراض النساء و التوليد بمستشفى الشاطبي الجامعي.

تم تقسيم هؤلاء المرضى عشوائيا باستخدام تقنية الظرف المغلق إلى ثلاث مجموعات متساوية (١٥ مريضا لكل مجموعة):

- المجموعة ١: تلقى المرضى فيها عقار البريجابالين (٧٥ ملجم) عن طريق الفم .
- المجموعة ٢: تلقى المرضى فيها عقار البريجابالين (١٥٠ ملجم) عن طريق الفم .
- المجموعة ٣: تلقى المرضى فيها العقار المموه "كبسولات فارغة" عن طريق الفم.

بعد موافقة خطية من كل مريض تم عمل تقييم ما قبل العملية لجميع المرضى من خلال أخذ تاريخ مرضي مفصل، فحص إكلينيكي كامل، تقييم للممرات الهوائية و الفحوص المختبرية الروتينية. ثم تلقى كل مريض عقار البريجابالين ٧٥ أو ١٥٠ مجم أو العقار المموه عن طريق الفم ساعة قبل دخول العملية.

لدى وصول المريض الى غرفة العمليات، تم توصيله بأجهزة القياس الأساسية، بما في ذلك رسم القلب، قياس ضغط الدم الشرياني الغير إختراقي ونسبة تشبع الدم الشرياني بالأكسجين.

وقد خضع جميع المرضى لنفس بروتوكول التخدير كالتالي:-

بدأ التخدير الكلي بإعطاء عقار الفنتانيل بجرعة ٢ ميكروجم/ كجم تليها بخمسة دقائق عقار الزيلوكين بجرعة ١ ملجم/ كجم تليها بدقيقة عقار البروبوفول ١٪ بجرعة ٢ ملجم / كجم تليها جرعة ٠,٢ ملجم / كجم من عقار السيزأتراكيوريم عن طريق الوريد لتسهيل القيام بتنبيب القصبة الهوائية. وقد تم المحافظة على استمرار التخدير الكلي باستخدام عقار الأيزوفلورين ١-١,٥٪ في اوكسجين بنسبة ١٠٠٪ مع إعطاء جرعات إضافية من عقار السيزأتراكيوريم بجرعة ٠,٢ ملجم / كجم كل نصف ساعة حتى انتهاء العملية.

القياسات:

- معدلات الدورة الدموية وتشمل: معدل ضربات القلب، متوسط ضغط الدم الشرياني وتشبع الأكسجين الشرياني. والتي تم قياسها قبل التخدير الكلي وبعده كل ١٥ دقيقة على مدار العملية نزع أنبوبة القصبة الهوائية بعد العملية كل ٦ ساعات وحتى نهاية الدراسة.
- آلام ما بعد العملية الجراحية: وقد تم قياس الألم أثناء الراحة (مستقر) و في أثناء السعال (متحرك) بمقياس VAS. بدأ تقييم الألم عند وصول المريض إلى غرفته (٠) ومن ثم كل ٣٠ دقيقة في أول ساعتين، ثم كل ساعة حتى ست ساعات ثم كل ٦ ساعات حتى نهاية الدراسة (٢٤ ساعة). أيضا تم تسجيل مجموع الجرعات المطلوبة من عقار كيترولاك في خلال ال ٢٤ ساعة الأولى.
- مستوى السكون: تم تقييمه باستخدام مقياس السكون رامزي. عند وصول المريض إلى غرفته بعد العملية (٠) ثم كل ست ساعات حتى نهاية الدراسة (٢٤ ساعة).
- تم ملاحظة الغثيان والقيء خلال ال ٢٤ ساعة بعد العملية.
- كما تم ملاحظة أي آثار جانبية أخرى من عقار بريجابالين خلال ال ٢٤ ساعة الأولى بعد العملية الجراحية.

وكانت نتائج الدراسة كالتالي:-

- فيما يتعلق بالعلامات الحيوية، مقارنة بين المجموعات الثلاثة تبعا لمعدل نبضات القلب قد أوضحت اتقاها ملحوظا في مرضى المجموعة الثالثة وذلك في القياسات التالية بعد التخدير وبعد ١٥ دقيقة وبعد ٣٠ دقيقة و ٤٥ دقيقة و بعد ٦٠ دقيقة و بعد ٧٥ دقيقة و بعد ازالة الانبوبة الحنجرية و بعد مرور ١٢ و ١٨ ساعة ، وقد توافقت قياسات متوسط ضغط الدم الشرياني مع زيادة أيضا قياسه بعد ٢٤ ساعة.
 - فيما يتعلق بالآلام ما بعد العملية الجراحية في وضع السكون و الحركة، مقارنة بين الثلاث مجموعات قد أوضحت زيادة ملحوظة في شدة الألم في المجموعة الثالثة عند القياسات التالية عند الفترة المبكرة بعد العملية و بعد ٣٠ ، ٦٠ ، ٩٠ ، ١٢٠ ، دقيقة و بعد ٣ ، ٤ ، ٦ ، ١٤ ، ٢٠ ، ساعة.
 - و بالتالي فان مرضى المجموعة الثالثة أيضا أضحوا زيادة ملحوظة في جرعة المسكنات على مدار ٢٤ ساعة بعد العملية و أيضا في احتياجهم للمسكن في وقت مبكر عن مرضى المجموعتين الاخرين.
 - فيما يتعلق بمستوى السكون، على حسب درجة الوعي و ذلك من خلال مقياس السكون رامزي فان مرضى المجموعتين الاولى و الثانية أظهروا درجة وعي أقل في الفترة المبكرة بعد العملية.
 - اما بالنسبة للآثار الجانبية، فلم يكن هناك اختلاف ذات دلالة إحصائية بين المجموعات الثلاث من حيث الغثيان و القيء و اي اثر جانبي اخر خلال ال ٢٤ ساعة بعد العملية.
- وقد أكدت هذه الدراسة على أن جرعة ١٥٠ ملجم أكثر فاعلية من جرعة ٧٥ ملجم قبل العملية في استقرار العلامات الحيوية وتخفيف الآلام بعد العملية و على تخفيض الجرعة الكاملة من المسكنات و تاخير اول جرعة منها و ان الجرعتين لم يحدثوا اي اعراض جانبية.

وبالتالي وفي ضوء النتيجة السابقة، يمكن أن نوصي بالاتي:

١. الحاجة إلى المزيد من الدراسات لتحديد الجرعة المناسبة من عقار البريجابالين التي من الممكن ان تؤثر على الحد من الغثيان و القيء مع المحافظة على نفس تأثيرها على آلام ما بعد العملية و دون زيادة في اعراضه الجانبية في نفس نوعية هذه العمليات.
٢. الحاجة إلى المزيد من الدراسات لتحديد أفضل جرعة والتوقيت المناسبة من عقار البريجابالين التي يمكن استخدامها للسيطرة على الآثار المصاحبة لتثبيت القصبة الهوائية والتي تساعد على استقرار العلامات الحيوية والتنفس وجعلها آمنة سواء أثناء أو ما بعد العمليات الجراحية.
٣. الحاجة إلى مزيد من الدراسات للتوسع في استخدام عقار البريجابالين في تخفيف الألم ما بعد الجراحة وتقليل استخدام المواد الأفيونية في العمليات الجراحية الأخرى التي تعتبر أكثر إيلاما أو قد تحتاج الى استهلاك أكثر من المسكنات.

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مقدمة من

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بكالوريوس الطب والجراحة - جامعة الإسكندرية، ٢٠٠٩

للحصول على درجة

الماجستير

فى

التخدير والعناية المركزة الجراحية

موافقون

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رسالة علمية

مقدمة إلى كلية الطب - جامعة الإسكندرية
إستيفاء للدراسات المقررة للحصول على درجة

الماجستير

فى

التخدير والعناية المركزة الجراحية

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٢٠١٥