RECOMMENDATIONS

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From the current study, we recommend the following:

1. The addition of dexmedetomidine to intrathecal bupivacaine can be a good alternative to the use of intrathecal fentanyl in spinal anaesthesia.
2. Further studies on large scale of patients and different age groups should be promoted to support the efficacy and safety of adding dexmedetomidine to intrathecal bupivacaine in spinal anaesthesia.
3. Further studies on different doses of dexmedetomidine should be promoted to reach the optimum dose for the use in addition to intrathecal bupivacaine in spinal anaesthesia.

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PROTOCOL

A COMPARATIVE STUDY OF INTRATHECAL DEXMEDETOMIDINE AND FENTANYL AS ADDITIVES TO BUPIVACAINE

دراسة مقارنة لإعطاء ديكسميديتوميدين أوفينتانيل كعقاقيرمضافة لعقارالبيوبيفاكين تحت الأم الجافية

Protocol of a thesis submitted

to the Faculty of Medicine

University of Alexandria

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and Surgical Intensive Care

by

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خطة بحث مقدمة

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جامعة الإسكندرية

إيفاء جزئيا

لشروط الحصول على درجة

الماجستير فى التخدير

والعناية المركزة الجراحية

من

وفاء حسن أحمد

بكالوريوس الطب و الجراحة

طبيب مقيم

مستشفيات جامعة الإسكندرية

قسم التخدير

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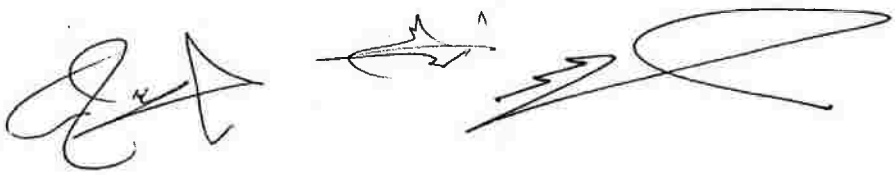


INTRODUCTION

Lower abdominal and lower limb surgeries may be performed under local, regional (spinal or epidural) or general anaesthesia, but neuraxial blockade is the preferred mode of anaesthesia. Spinal block is still the first choice because of its rapid onset, superior blockade, low risk of infection as from catheter in situ, less failure rates, and cost effectiveness, but has the drawbacks of shorter duration of block and lack of postoperative analgesia. [1]

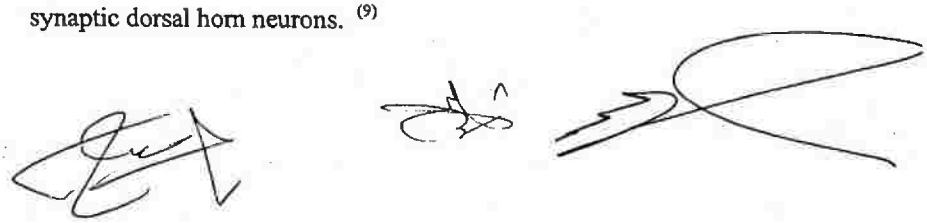
The choice of local anaesthetic agent and its concentration is determined by the anticipated duration of the surgical procedure and the balanced need for sensory and motor block. [2]

Bupivacaine is an amide local anaesthetic with slow onset and long duration of action (lasting 2-2.5 hours). [3] Large doses of intrathecal bupivacaine were associated with severe hypotension and delayed recovery of the motor block. [4]

In recent years, the use of intrathecal adjuvants has gained popularity with the aim of prolonging the duration of block, better success rate, patient satisfaction, decreased resource utilization compared with general anaesthesia, and faster recovery. The quality of the spinal anaesthesia has been reported to be improved by the addition of opioids (such as morphine, fentanyl, and sufentanyl). Other drugs (such as dexmedetomidine, clonidine, magnesium sulfate, neostigmine, ketamine and midazolam) have been studied to improve the quality of spinal anaesthesia, but uptill now there is no single drug with no side effects. [5]

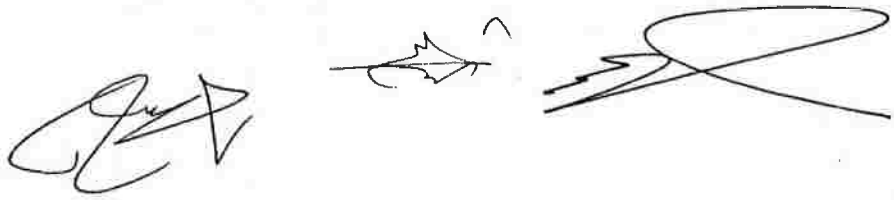
Fentanyl is one of the short acting narcotic analgesics with potent morphine-like action. It produces many of its clinical effects rapidly after intrathecal administration. [6] Neuroaxial administration of lipophilic opoids such as, fentanyl and sufentanyl tends to provide a rapid onset of analgesia and their rapid clearance from cerebrospinal fluid (CSF) may limit cephalic spread and the development of certain side effects such as, delayed respiratory depression. [7]

Dexmedetomidine, a new highly selective alpha 2 agonist, is under evaluation as a neuraxial adjuvant as it is supposed to provide stable hemodynamic conditions, good quality of intraoperative and prolonged postoperative analgesia with minimal side effects. It is FDA (Food and Drug Administration) approved as a short term sedative for mechanically ventilated intensive care unit patients. [8] The analgesic action of intrathecal alpha 2 adrenoceptor agonist is supposed to be by depressing the release of C-fiber transmitters and by hyperpolarization of post-synaptic dorsal horn neurons. [9]



AIM OF THE WORK

The aim of this study is to compare the addition of either dexmedetomidine or fentanyl to intrathecal bupivacaine as regards: the onset and duration of sensory and motor block, hemodynamic effects, postoperative analgesia and adverse effects of either drugs.

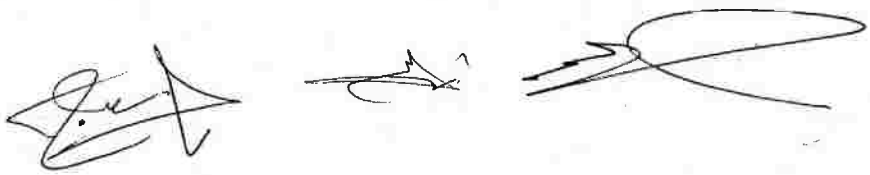


PATIENTS

The present study will be carried out on 60 patients (approved to be sufficient by the department of statistics, High Institute of Public Health, University of Alexandria), aged 18-50 years old, of both sexes, of height ranging from 160-190cm [1], with American Society of Anaesthesiologists (ASA) I and II health status, admitted to the Alexandria Main University Hospitals and scheduled for elective lower abdominal or lower limb surgeries.

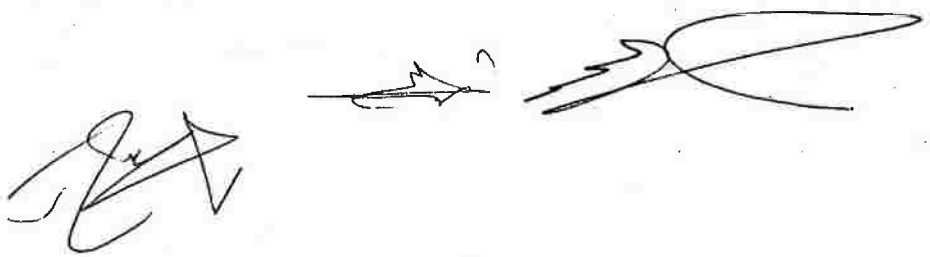
Exclusion criteria will include:

1. Pregnant and lactating females.
2. Patients allergic to studied medications.
3. Patients with heart block & dysrhythmias.
4. Hypertensive patients.
5. Patients on therapy with adrenergic receptor antagonist, calcium channel blocker, &/or angiotensin converting enzyme (ACE) inhibitor.
6. Patients with opium addiction & sedative drugs consumption.
7. Patients with contraindications for spinal anaesthesia.



Patients will be randomly categorized by closed envelope method in a double blinded study into three equal groups (20 patients each): [10]

- **Group B:** Patients will receive 3ml (15mg) of 0.5% hyperbaric bupivacaine + 0.5ml of normal saline intrathecally.
- **Group F:** Patients will receive 3ml (15mg) of 0.5% hyperbaric bupivacaine + 0.5ml (25 microgram) of preservative free fentanyl intrathecally. [11]
- **Group D:** Patients will receive 3ml (15mg) of 0.5% hyperbaric bupivacaine + 0.5ml (5 microgram) of diluted, preservative free dexmedetomidine intrathecally. [12,13]



METHODS

After the approval of the local ethical committee, consent will be taken from each patient confirming his/her acceptance of intrathecal anaesthesia, after knowing the technique and its possible complications.

Pre-operative screening of all patients will include:

- History taking.
- Complete physical examination.
- Laboratory investigation:
    1. Complete Blood Picture.
    2. Prothrombin time, activated partial thromboplastin time and INR.
    3. Liver enzymes: Aspartate transaminase, Alanine transaminase.
    4. Serum urea and creatinine.
    5. Fasting Blood Sugar.

Patients will be premedicated by H_2 antagonist (ranitidine 50mg, intramuscularly, 2 hours preoperatively). Before commencing regional anaesthesia, standard monitoring will be established using multichannel monitor (Hewlett-Packard, Viridia 24, Germany) as follow:

- Electrocardiogram (ECG) for heart rate and rhythm. (Beat/min).
- Non-invasive measurement of arterial blood pressure. (Mean blood pressure in mmHg).
- Oxygen saturation. (SpO2%).

They will be given intravenous lactated Ringer's solution 10 ml/kg as volume preload. Spinal anesthesia will be performed in the sitting position at the L3-4 interspace with midline or paramedian approach by using a 25 gauge Quinke's

spinal needle with all aseptic precautions. Injection will be according to the following groups:

- Group B: Patients will receive 3ml (15mg) of 0.5% hyperbaric bupivacaine + 0.5ml of normal saline intrathecally.
- Group F: Patients will receive 3ml (15mg) of 0.5% hyperbaric bupivacaine + 0.5ml (25 microgram) of preservative free fentanyl intrathecally.
- Group D: Patients will receive 3ml (15mg) of 0.5% hyperbaric bupivacaine + 0.5ml (5 microgram) of diluted, preservative free dexmedetomidine intrathecally.

Injection will be given over 10-15 sec, immediately after completion of the injection patients will lie supine. Low flow oxygen (4L/minute) will be administered via oxygen mask.

MEASUREMENTS

The following parameters will be measured:

I. **Patient data:**
1- Patient's age (years).

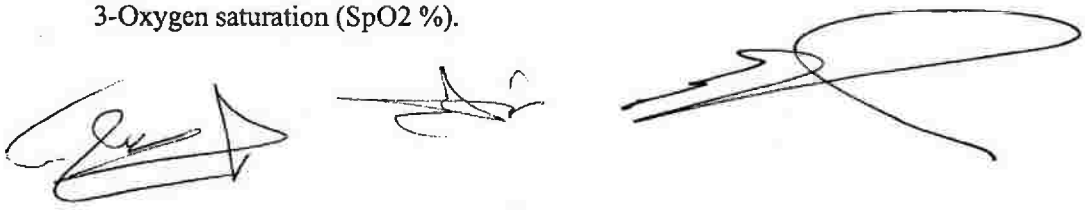
2- Patient's height (cm).

II. **Duration of the operation:** (minutes).

III. **Hemodynamic measurements:**
1-Heart rate (HR in beat / min).

2-Non-invasive measurement of mean arterial blood pressure (MABP in mmHg).

3-Oxygen saturation (SpO2 %).



All previous parameters will be continously monitored and recorded at the following periods:

1- Before spinal anaesthesia.

2- Immediate after spinal analgesia and every 15 minutes, for 90 min and at the end of surgery.

3- Every hour for 6 hours postoperative.

IV. Assessment of sensation:

All durations will be calculated considering the time of spinal injection as time zero.

Sensory analgesia will be assessed by iced cubes to measure the following:

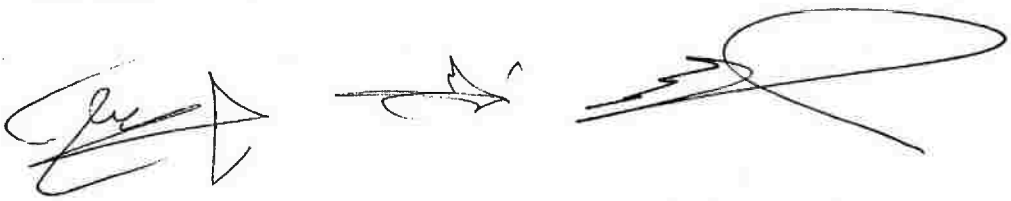
1- Onset of sensory analgesia (defined as time in minutes to reach highest sensory level) tested every minute after intrathecal injection till reaching the highest level).

2- Sensory level of analgesia (defined as segmental level of highest sensory analgesia).

3- Duration of analgesia (defined as the time in minutes it takes for sensory level to decrease to dermatomal level S1) measured from the highest obtained sensory level every 15 minutes. [1]

Postoperatively:

4- Pain intensity will be evaluated by using a visual analogue scale (VAS) starting from the first pain experienced by the patient till the end of study with 0 corresponding to no pain and 10 to the worst pain imaginable, it will be assessed at the first, second, forth, sixth, eighth, hour and every four hours till 24 hours.[14]



5- Time for first request of analgesia (defined as the time elapsed from the time of spinal injection till reaching VAS>4) will be recorded and treated by intramuscular diclofenac sodium in a dose of 1mg/kg to be repeated if needed after 12 hours but if pain persists after one hour from the first dose, 25 mg pethidine will be given intravenously. [10]

6- The total analgesic dose of both diclofenac sodium and pethidine taken within the first 24 hours will be recorded.

V. Assessment of motor function:

Motor blockade will be evaluated as follows:

1- Onset of motor block. (Defined as time in minutes from the end of drug injection intrathecally until patient is unable to move hip, knee and ankle) [15] tested every minute after intrathecal injection.

2- Duration of motor block in minutes will be recorded from the time of the onset of the block to the time when the patient will be able to lift their legs in bed against gravity (Bromage-score 0) tested every 15 min. This is according to the following modified Bromage-score: [16]

0: The patient is able to move the hip, knee and ankle.

1: The patient is unable to move the hip but is able to move the knee and ankle.

2: The patient is unable to move the hip and knee but able to move the ankle.

3: the patient is unable to move hip, knee or ankle.

VI. Side effects:

The incidence of adverse effects such as hypotension, bradycardia, nausea, vomiting, shivering, pruritus, respiratory depression and sedation will be recorded.

Hypotension, defined as a decrease of systolic blood pressure by more than 30% from baseline or fall below 90mmHg, will be treated by intravenous fluids and intravenous increments of 5mg ephedrine. Total ephedrine dose will be recorded.

Bradycardia, defined as heart rate less than 50bpm, will be treated by 0.6mg of intravenous atropine

Respiratory depression, defined as respiratory rate <10, will be assessed for any needed airway support.

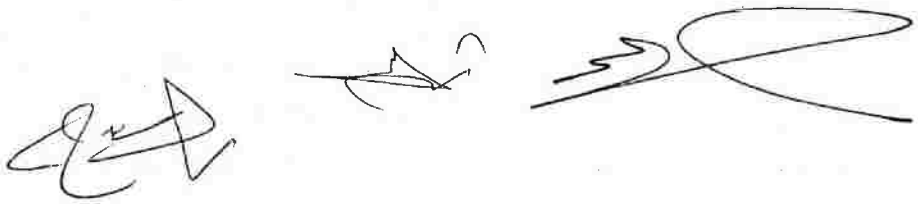
Sedation will be assessed by Ramsay Sedation Score. [17] This will also be assessed for any needed airway support.

Score	Response
1	Anxious or restless or both
2	Cooperative, oriented and tranquil
3	Responding to commands
4	Brisk response to stimulus
5	Sluggish response to stimulus
6	No response to stimulus

These side effects will be assessed at the first, second, forth, sixth, eighth, hour and every four hours till 24 hours.

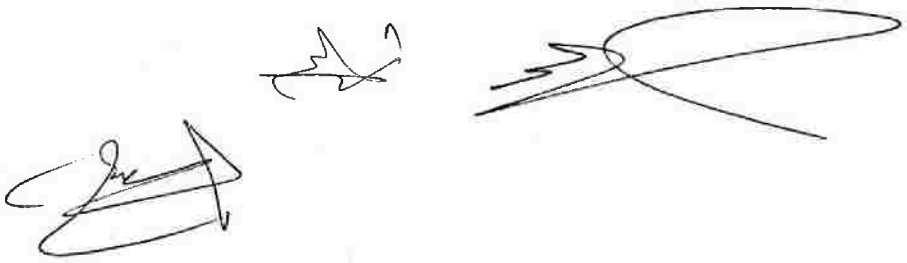
RESULTS

The results of this study will be tabulated and statistically analyzed according to the collected data to fulfill the aim with the aid of different ways of presentation: numerical, mathematical and graphical.



DISCUSSION

Findings will be discussed in view of the results of the work and their scientific significance.



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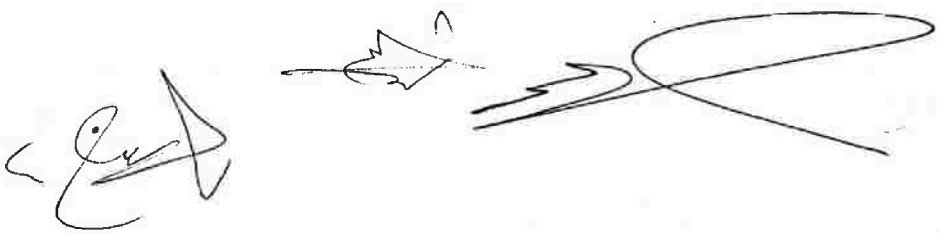

SAMPLE SIZE:

Using a power of 80% to detect a significant difference in mean time for sensory regression to S1 from highest sensory level between a group of patients undergoing lower abdomen or lower limb surgery and receiving dexmedetomidine and others receiving fentanyl = 289 minutes, [1] standard deviations are 20 minutes and 12.3 minutes, respectively, alpha error = 0.05, using the sample ratio between groups = 1. The minimal required sample size was found to be 45 which mean 15 for each group.

The total sample will be randomly selected & equally allocated among the study groups.

The sample size was calculated using G power software [2].

Reference:

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ARABIC SUMMARY

الملخص العربى

جعلت بساطة أسلوب التخدير الشوكي وموثوقيتها واحدة من التقنيات المفضلة في جراحات أسفل البطن و الأطراف السفلى. ولكن فى حالة انتهاء تأثير التخديرالشوكى غيرالمتوقع في وقت مبكر أو طول مدة العملية يمكن أن يسبب الألم أثناء العملية. و لذلك فإن زيادة جرعة التخدير الموضعي، أو إضافة المواد الأفيونية للتخدير الشوكي قد تكون مفيدة لإطالة مدة التخدير ولكن قد تتسبب في عدم استقرار الديناميكية الدموية، والغثيان، واحتباس البول، وخمول فى الجهاز التنفسي وتأخرعودة الحركة فى الأطراف السفلى، ولذلك برزت الحاجة إلى عقارات مكملة للعقارات الموضعية.

وكان **الهدف** من هذه الدراسة هو مقارنة إضافة عقار الديكسميديتوميدين أو الفنتانيل إلى عقار البيوبيفاكين فى التخدير الشوكى بشأن ما يلي: بداية تأثير العقارعلى الإحساس و الحركة، ومدة تأثيره على الإحساس و الحركة وتأثيره على العلامات الحيويه، و تأثيره على تسكين الألم و على حدوث المضاعفات.

وقد أجريت الدراسة على ٦٠ مريضا داخل مستشفيات جامعة الإسكندرية والمقرر عقدها في جراحات أسفل البطن والأطراف السفلى . تم تقسيمهم إلى ثلاث مجموعات:

المجموعة (ب): تم إعطاء المرضى ٣ ميللى (١٥ مجم) من عقار البيوبيفاكين (عالى الكثافة) ٠,٥% + ٠,٥ ميللى من محلول الملح الطبيعى داخل الأم الجافية.

المجموعة (ف): تم إعطاء المرضى ٣ ميللى (١٥ مجم) من عقار البيوبيفاكين (عالى الكثافة) ٠,٥% + ٠,٥ ميللى(٢٥ ميكروجرام) من عقار الفينتانيل (الخالى من المواد الحافظة) داخل الأم الجافية.

المجموعة (د): تم إعطاء المرضى ٣ ميللى (١٥ مجم) من عقار البيوبيفاكين (عالى الكثافة) ٠,٥% + ٠,٥ ميللى (٥ ميكروجرام) من عقار الديكسميديتوميدين المخفف (الخالى من المواد الحافظة) داخل الأم الجافية.

تم تقييم المرضي قبل اجراء التدخل الجراحي عن طريق السؤال عن التاريخ المرضي و توقيع الكشف الاكلينيكي و اجراء التحاليل والفحوصات الطبية.

تم إعطاء المرضى أدوية مضادة لحموضة المعدة فى تحضيرما قبل العملية. تم توصيل المرضى بأجهزة لقياس العلامات الحيوية قبل اجراء التخدير الشوكي و كانت عبارة عن رسم قلب لمعرفة معدل النبض ، متوسط ضغط الدم الشريانى، نسبة تشبع الدم الشريانى بالأكسجين.

تم إعطاء المرضى محلول رينجر الوريدى (١٠ ميللى لكل كيلوجرام). تم إعطاء التخدير الشوكى فى وضع الجلوس بين الفقرة القطنية الثالثة و الرابعة فى منتصف الجسم أو محاز للوسط بواسطة إبرة بزل (كوينكى) مقاس ٢٥ مع أخذ كل إحتياطيات التعقيم و تم حقن العقارات، كل حسب مجموعته. تم استلقاء المرضى على ظهورهم عقب إعطاء التخدير الشوكى و تم توصيل الأوكسيجين (٤لتر/الدقيقة) لهم بواسطة قناع الأوكسيجين.

تم قياس البيانات التالية:

بيانات المريض: ١-السن(بالسنوات) ٢-الطول(بالسنتيمترات). **مدة العملية:** (بالدقائق). **العلامات الحيوية** (قبل و أثناء و بعد العملية): معدل النبض، متوسط ضغط الدم الشريانى، نسبة تشبع الدم الشريانى بالأكسجين.

تم دراسة **الغلق العصبى** عن طريق : قياس بداية فقدان الإحساس، أعلى مستوى لفقدان الإحساس ومدة فقدان الإحساس. كما تم قياس تسكين الألم بعد العملية وتم قياسه عن طريق تحديد درجة الألم باستخدام تدريج المقياس المرئى ،و أيضا تم تقدير المدة التى احتاج المريض بعدها للمسكنات وجرعة المسكنات التى تناولها المريض فى الأربعة والعشرين ساعة الأولى بعد العملية.

دراسة الأثر على **الارتخاء العضلى** عن طريق : قياس بداية فقدان الحركة و مدة فقدان الحركة.

كذلك تم ملاحظة وتسجيل **المضاعفات** التى حدثت أثناء وبعد العملية.

لوحظ من هذه الدراسة الآتى: عدم وجود تغيرات ملحوظة بين المجموعات بالنسبة إلى السن، الطول، الجنس، مدة العملية أو الحالة الصحية العامة.

كان هناك إنخفاض إحصائى ملحوظ فى معدل النبض عند الدقيقة ٤٥ فى المجموعة (د) عن المجموعة (ف) (بدلالة إحصائية=٠,٠٤٥) كما تكرر ذلك عند الدقيقة ٦٠ و٩٠ (بدلالة إحصائية=٠,٠٢٧ و ٠,٠٤٧ بالتوالى) فقط. بمقارنة المجموعة (ف) و (ب) كان الإنخفاض فى المجموعة (ب) عند الدقيقة ٣٠ و ٤٥ (بدلالة إحصائية=٠,٠٤٠ و ٠,٠٤٨ بالتوالى).

بالنسبة لمتوسط ضغط الدم الشريانى كان هناك إنخفاض إحصائى فى المجموعة (د) عن المجموعة (ف) عند الدقيقة ٤٥ (بدلالة إحصائية=٠,٠٣١) و كان هناك إنخفاض إحصائى فى المجموعة (ب) عن المجموعة (د) بعد إعطاء التخدير الشوكى و عند الدقيقة ١٥ (بدلالة إحصائية=٠,٠٠٦ و ٠,٠٤٤) وأيضا فى المجموعة (ب) عن المجموعة (ف) بعد إعطاء التخدير الشوكى و عند الدقيقة ١٥ (بدلالة إحصائية=٠,٠٠٣ و ٠,٠٥٠ بالتوالى).

لم يكن هناك أى اختلاف إحصائى بين المجموعات بالنسبة لنسبة تشبع الدم الشريانى بالأكسجين.

أما بالنسبة لبداية فقدان الإحساس فكانت نتائج المجموعة (د) الأسرع بالمقارنة بالمجموعتين الأخرتين (دلالة إحصائية =٠,٠٠٠)

أما بالنسبة لبداية فقدان الحركة فكانت نتائج المجموعة (د) الأسرع بالمقارنة بالمجموعتين الأخرتين (دلالة إحصائية =٠,٠٠) كما كانت نتائج المجموعة (ف)أسرع من المجموعة (ب) (بدلالة إحصائية= ٠,٠١٦)

كانت مدة فقدان الإحساس و مدة فقدان الحركة لفترة أطول فى المجموعة (د) بالمقارنة بالمجموعة (ف) (بدلالة إحصائية =٠,٠٠٠) و أيضا كانت نتائج المجموعة (ف) أطول من المجموعة (ب) (بدلالة إحصائية =٠,٠٠٠)

كانت قراءات تدريج المقياس المرئى فى المجموعة (د) منخفضة عن المجموعتين الأخرتين كما كانت منخفضة فى المجموعة (ف) عن المجموعة (ب).

احتاج عدد أقل إلى المسكنات فى المجموعة (د) عن فى المجموعتين الأخرتين و كان ذلك فى وقت متأخر عن المجموعة (ف) و (ب) (بدلالة إحصائية=٠,٠١٣و٠,٠٠٢ بالتوالى). احتاج عدد أقل إلى المسكنات فى المجموعة (ف) عن المجموعة (ب) و كان ذلك فى وقت متأخر عنها (بدلالة إحصائية=٠,٠١٥). لم يكن هناك احتياج لأى مسكنات فى المجموعة (د) بنسبة ٧٥% و فى المجموعة (ف) ٥٠% و فى المجموعة (ب) ١٠%.

احتاجت مرضى المجموعة (د) إلى جرعات أقل من مسكن الديكلوفيناك صوديوم عن المجموعتين الأخرتين (بدلالة إحصائية=٠,٠٣٠ و ٠,٠٠٠ بالتوالى) و كذلك كان احتياج المجموعة (ف) أقل من المجموعة (ب) (بدلالة إحصائية=٠,٠٠٠)

لم يحتاج مرضى المجموعة (د) إلى مسكن البيثيدين. و كذلك كان احتياج مرضى المجموعة (ف) لجرعات أقل من المجموعة (ب) من نفس العقار (بدلالة إحصائية=٠,٠٢٦).

لم يكن هناك أى اختلاف إحصائى بين المجموعات بالنسبة لحدوث المضاعفات و هى قلة معدل النبض، انخفاض فى ضغط الدم،الغثيان، القئ، الرعشة، الحكة، هبوط معدل التنفس و انخفاض درجة الوعى. كما لم يكن هناك أى اختلاف إحصائى بين المجموعات بالنسبة لجرعات عقارى الأتروبين و الإفدرين.

الاستنتاجات:

١. بداية فقدان الإحساس و الحركة أسرع عند استخدام ٥ ميكروجرام من عقار الديكسميديتوميدين من استخدام ٢٥ ميكروجرام من عقار الفينتانيل داخل الأم الجافية بالإضافة إلى عقار البيوبيفاكين.
٢. مدة فقدان الإحساس و الحركة أطول عند استخدام ٥ ميكروجرام من عقار الديكسميديتوميدين من استخدام ٢٥ ميكروجرام من عقار الفينتانيل داخل الأم الجافية بالإضافة إلى عقار البيوبيفاكين.
٣. أدى استخدام عقار الديكسميديتوميدين داخل الأم الجافية بالإضافة إلى عقار البيوبيفاكين إلى تسكين الألم لفترة أطول بعد انتهاء العملية.
٤. استخدام عقار الديكسميديتوميدين داخل الأم الجافية بالإضافة إلى عقار البيوبيفاكين أدى إلى احتياج أقل من المسكنات فى فترة ما بعد العملية.
٥. لم يؤدى استخدام عقار الديكسميديتوميدين أو عقار الفينتانيل داخل الأم الجافية بالإضافة إلى عقار البيوبيفاكين إلى أى خمول فى درجة الوعى.
٦. كانت المضاعفات قليلة و مقبولة عند استخدام عقار الديكسميديتوميدين.

التوصيات:

١- إضافة عقار الديكسميديتوميدين إلى عقار البيوبيفاكين (عالى الكثافة) ٠,٥% يمكن أن يؤخذ فى الإعتبار كاستخدام روتينى فى التخدير الشوكى لإزالة الألم بالعمليات و بعدها.
٢- استكمال الدراسات المستقبلية لمعرفة مدى كفائة إضافة عقار الفينتانيل مع عقار الديكسميديتوميدين إلى عقار البيوبيفاكين (عالى الكثافة) ٠,٥% فى التخدير الشوكى بالنسبة لتحسين إزالة الألم.
٣- امكانية استخدام عقار الديكسميديتوميدين بحذر فى مجموعات عمرية مختلفة و فى أمراض طبية مختلفة و فى فترة الحمل.

الملخص العربى

لجنة الإشراف

أ. د./ أحمد محمد العطار .....
أستاذ التخدير والعناية المركزة الجراحية
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أ. د./ محمد شوقى عبد العليم .....
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مشرف مشارك

د./ رجب سعد بلتاجى .....
مدرس التخدير والعناية المركزة الجراحية
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دراسة مقارنة لإعطاء ديكسميديتوميدين أو فينتانيل كعقاقير مضافة لعقار البيوبيفاكين تحت الأم الجافية

مقدمة من

وفاء حسن أحمد

بكالوريوس الطب والجراحة - جامعة الإسكندرية، ٢٠٠٧

للحصول على درجة

الماجستير

فى

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أ. د /أحمد محمد العطار أستاذ التخدير والعناية المركزة الجراحية كلية الطب جامعة الإسكندرية	.....
أ. د / ماجدة محمد أبو علو أستاذ التخدير معهد البحوث الطبية جامعة الإسكندرية	.....
أ.د / وفاء عبد اللطيف شفشق أستاذ التخدير والعناية المركزة الجراحية كلية الطب جامعة الإسكندرية	.....

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رسالة علمية

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

الماجستير

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التخدير والعناية المركزة الجراحية

مقدمة من

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