

DISCUSSION

Induction of anaesthesia and tracheal intubation may cause profound alteration of haemodynamic state of the patient consequent to both the effects of anesthetic drugs administered preoperatively and the adrenergic state of the patient.

Stress response to laryngoscopy and intubation has always been concern especially for the cardiac patient.

Direct laryngoscopy and intubation produces maximum pressor response to the direct stimulation of pharyngeal structures⁽⁶²⁾. The pressor response may be especially deleterious in patients with preexisting myocardial ischemia and cerebral insufficiency.

The present study was carried to compare the effect of premedication with single oral dose of 150 mg pregabalin versus 0.2 mg clonidine on haemodynamic response to tracheal intubation and the level of preoperative sedation was also compared.

The study was done on 40 patients belonging to ASA I and ASA II classification divided into two groups:

Group I: Patients received 150 mg pregabalin orally 90 minutes before operation.

Group II: Patients received 0.2 mg clonidine orally 90 minutes before operation.

Comparison between the two groups as regards age and sex showed no statistical difference.

Comparison between the two groups as regards haemodynamics as heart rate and mean arterial blood pressure showed that clonidine and pregabalin effectively decreased the haemodynamic changes that occur during the stress response to endotracheal intubation (and this decrease didn't need any treatment).

Clonidine showed significantly more decrease of the rise in heart rate and mean arterial blood pressure than the pregabalin.

Similar to the present study Oddby-Muhrbeck et al⁽⁶³⁾, found in the study carried out on 68 patients undergoing breast cancer surgery under general anaesthesia that statistically significant difference in the heart rate and mean arterial blood pressure between the group that received clonidine and the group that received placebo. They explained their results on basis that clonidine decrease sympathetic flow.

Yu et al⁽⁶⁴⁾, investigated the clinical efficacy of oral clonidine premedication in anaesthesia and analgesia on 32 patients undergoing laparoscopic cholecystectomy, out of which 16 patients received 150 µg clonidine orally and the other 16 patients received placebo before anaesthesia. The authors found that oral clonidine provide a stable heart rate.

Yotsui⁽⁶⁵⁾, observed the systolic blood pressure lower in the clonidine group than in the placebo group immediately after endotracheal intubation and after extubation where clonidine group received 4 µg/ kg orally 2 hours before induction of anaesthesia.

Sung et al⁽⁶⁶⁾, investigated the clinical efficiency of oral clonidine premedication in anaesthesia and analgesia in patients undergoing laparoscopic cholecystectomy where the clonidine group were premedicated with oral clonidine 150 µg prior to anaesthesia. There was greater haemodynamic stability perioperative compared to placebo.

Singh and Arora⁽⁶⁷⁾ studied the clinical efficacy of oral clonidine premedication in patients undergoing laparoscopic cholecystectomies. Fifty patients scheduled for elective laparoscopic cholecystectomy under general anaesthesia were randomly allocated to receive premedication with either oral clonidine 150 µg or placebo 90 minutes prior to induction. Oral clonidine was found to be significantly better in terms of maintaining stable haemodynamics, having an isoflurane sparing effect and having a prolonged time interval to the first request of analgesia postoperatively compared to the control group. Administration of oral clonidine 150 µg as a pre-medicant in patients undergoing laparoscopic cholecystectomy resulted in improved perioperative haemodynamic stability and a reduction in the intra-operative anaesthetic and post-operative analgesic requirements.

Talebi et al⁽⁶⁸⁾ studied the efficacy of pre-anaesthetic orally administration of clonidine on pulse rate and blood pressure due to stress response of laryngoscopy and tracheal intubation. The clonidine group showed a significant superiority over placebo in the prevention of increase in systolic blood pressure as well as heart rate during the intubation.

Whitwam et al⁽⁶⁹⁾, found in a study carried out on 48 patients scheduled for day case surgery under general anaesthesia that there was significant difference in the heart rate and mean arterial blood pressure between those who received clonidine 4 µg/ kg iv prior to surgery and those who received placebo.

In the present study the haemodynamic stability of clonidine may be explained by⁽¹⁷⁾: sympatholysis mediated by the CNS alpha-2 adrenoceptor subtype. Alpha-2-adrenoceptor agonists appear to attenuate the CNS “set-point” at which blood pressure is regulated. The sustained decrease in blood pressure and heart rate are thought to be due to increased parasympathetic (vagal) activity, a centrally-mediated inhibition of the locus ceruleus adrenoceptors, or decreased norepinephrine release at the neuroeffector junction. Imidazoline receptors in the brainstem may also be involved in increasing vagal tone.

However, few data did address the correlation between pre-operative pregabalin administration and the reduction in haemodynamic pressor response to airway instrumentation, during different operative surgeries; of these, the one conducted by Gupta et al⁽⁷⁰⁾ in relation to elective laparoscopic cholecystectomy.⁽⁷¹⁾ All such studies did agree on the benefits of the drug, to significantly decrease the significant increase in heart rate and blood pressure provoked by the noxious painful and stressing stimuli of laryngoscopy and intubation^(70,71,72,73) Through different perspectives. More-over the attenuation was pertained stabilized with minimal haemodynamic fluctuations, where blood pressure remained significantly reduced throughout the intra-operative period.^(70,71)

The explanations set by Rastogi et al and Gupta et al for pregabalin utility in ameliorating such pressor responses were based on their simultaneous findings of pre-operative dose-related sedation induced by the drug in their study series.^(70, 71)

One is in favor to adopt reasoning the haemodynamic stability encountered, to the anxiolytic potentialities of pregabalin, raised in previous literature as that of Lauria-Horner and Pohl⁽⁷⁵⁾ and Baldwin et al.⁽⁷⁶⁾ This aside its pain ameliorating properties currently observed and previously established using the same tested pregabalin dose in different clinical trials as that of Agarwal et al,⁽⁷⁷⁾ Cabrera Schulmeyer et al,⁽⁷⁸⁾ and Freedman and O'Hara.⁽⁷⁹⁾

Also Sundar AS et al studied the effects of preemptive pregabalin on attenuation of stress response to endotracheal intubation and opioid sparing effect in patients undergoing off pump CABG, the study showed that a single oral dose of 150 mg pregabalin given one hour before surgery attenuated the pressor response in adults.⁽⁸⁰⁾

In the present study the haemodynamic stability of pregabalin may be explained by^(29,34,46,47).

Pregabalin transiently inhibit Ca influx, thereby reducing release of several neurotransmitters like glutamate, norepinephrine, serotonin, dopamine, substance P and CGRP.

Comparison between pregabalin and clonidine as regard sedation:

The present study found that both pregabalin and clonidine cause significant degree of sedation but pregabalin causes higher level of sedation than clonidine.

Similar to the present study White PF et al studied the effect of pregabalin on preoperative anxiety and sedation levels. The study showed pre operative pregabalin administration 75 mg to 300 mg oral increased pre operative sedation in dose related fashion.⁽⁸¹⁾

Gonano C et al studied the anxiolytic effect of pregabalin in outpatient undergoing minor orthopaedic surgery.the study showed that single preoperative dose of 300 mg pregabalin reduced anxiety in these patients.⁽⁸²⁾

In the present study this may be explained by presynaptic inhibition of ca influx causing decrease release of several neurotransmitters like glutamate, norepinephrine, serotonin, dopamine, substance P and CGRP^(29,34,46,47).

Similar to the present study Fanini et al⁽⁸³⁾ in their clinical trial, 40 patients, aged 16-64 year, underwent conservative, or prosthetic, or dental surgery procedures, received placebo or 150 micrograms of oral clonidine 90 min before the estimated time of induction of local anesthesia.. Clonidine produced significant sedation as well as significant difference in postoperative pain scores compared to placebo. Systolic blood pressure decreased significantly only after 120 to 150 min following clonidine pretreatment, but none of the patients were treated for hypotension.

Macpherson et al⁽⁸⁴⁾ studied the effect of 300 mcg oral clonidine versus 200 mg oral labetalol in laparoscopic cholecystectomy they found that the sedation score significantly raised in the clonidine group compared to the labetalol group.

Laurito CE et al studied the effectiveness of oral clonidine as a sedative /anxiolytic and as a drug to blunt the haemodynamic response to laryngoscopy, the study concluded

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that oral clonidine 0.2 mg was effective in reducing the level of behavioral and haemodynamic responses pre operatively and in blunting systolic hypertension produced by laryngoscopy⁽⁸⁵⁾

Kumkum gupta studied oral premedication by clonidine for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy and found that pregabalin and clonidine caused sedation and anxiolysis with hemodynamic stability.⁽⁷¹⁾

In contrast to the present study Singh and arura ⁽⁶⁷⁾ found that no significant difference of the sedation score between oral clonidine and the placebo group this may be explained by a smaller dose of clonidine (150 µg) used in that study.

Also, Samantary et al ⁽⁸⁶⁾ found in their study that there was no significant difference of the sedation score between oral clonidine and the placebo group. This may be explained by time of sedation score assessment was done after prolonged time than the present study.

SUMMARY

Induction of anaesthesia and tracheal intubation may cause profound alteration of haemodynamic state of the patient consequent to both the effects of anesthetic drugs administered preoperatively and the adrenergic state of the patient.

Stress response to laryngoscopy and intubation has always been concern especially for the cardiac patient.

Pregabalin, is one of these drugs that is coming into focus. It is a structural derivative of the inhibitory neurotransmitter GABA although it doesn't bind to its receptors or to that of benzodiazepines. It was originally developed as spasmolytic agents. Its anticonvulsant anxiolytic and sleep modulating utility permitted its use as an adjuncts for management of generalized or partial epileptic seizures resistant to conventional therapies. It is well tolerated with good safety profile and minimal adverse events most commonly being dizziness and somnolence.

Clonidine is classified as an imidazoline derivative. It is the prototypical alpha-2 receptor agonist. Its primary effect is at central pre- and postsynaptic alpha-2 receptors. It has an alpha-2 to alpha-1 selectivity ratio of 200:1. Clonidine has a half-life of 8 hours, and it is available for oral, transdermal, intramuscular, epidural, and intravenous administration

The present study was carried to compare the effect of premedication with single oral dose of 150 mg pregabalin versus 0.2 mg clonidine on haemodynamic response to tracheal intubation and the level of preoperative sedation was also compared.

The study was done on 40 patients belonging to ASA I and ASA II classification. They were randomly divided into two groups:

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Clonidine showed significantly more decrease in heart rate and mean arterial blood pressure than the pregabalin.

Comparison between pregabalin and clonidine as regard sedation:

The present study found that both pregabalin and clonidine cause significant degree of sedation but pregabalin causes higher level of sedation than clonidine.

CONCLUSION

1. Premedication with 150 mg oral pregabalin or 0.2 mg oral clonidine in ASA I and ASA II patients had been found to be relatively safe and effective method to protect against stress response triggered by laryngoscopy.
2. Oral clonidine is better than oral pregabalin in decrease the haemodynamic changes that occur in response to endotracheal intubation.
3. Oral pregabalin is better than oral clonidine in preoperative sedation.

RECOMMENDATIONS

- 1- 0.2 mg oral clonidine or 150 mg pregabalin can be recommended as premedication for all surgeries using general anaesthesia in healthy patients.
- 2- Further studies are required to find out the efficacy of these drugs in elderly patients, ASA III, IV patients particularly with compromised cardiovascular and neurological function.
- 3- The need for more clinical studies to identify the analgesic role of these drugs.
- 4- Further studies to identify the post operative side effects of these drugs.
- 5- Further studies to identify the efficacy of different doses of these drugs.

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المخلص العربي

تنبيب القصبه الهوائيه هي تقنيه آمنه و بسيطه و سريعه تهدف الى المحافظه على بقاء الممرات الهوائيه مفتوحه و حمايه الرئتين من دخول بقايا محتويات المعده وكذلك هي ضروريه لوضع المريض على جهاز التنفس الصناعى.

ولكن التنبيب الرغامى يتسبب فى ارتفاع ضغط الدم و تسارع نبضات القلب و عدم انتظامها و ارتفاع ضغط المخ . بالرغم من أن هذه الآثار قصيره المدى و لكنها قد تتسبب فى أضرار بالغه لمرضى القلب و الأوعيه الدمويه و مرضى المخ و الأعصاب.

لذلك تم عمل الكثير من الأبحاث العلميه للتوصل لكيفيه تقليل مثل هذه الآثار من ضمنها:

- ١ . تقليل وقت التنبيب الرغامى لأقل فتره ممكنه.
- ٢ . استخدام مخدر موضعى للممرات الهوائيه.
- ٣ . إعطاء جرعات من المواد الأفيونيه مثل الفيتانيل .
- ٤ . إعطاء أدويه ذات تأثير على القلب و الأوعيه الدمويه مثل عقار إزمولول و عقار نيكارديين .

و الدراسه الآتية تركز على تأثير عقارين هما البريجابالين و الكلونيدين.

عقار البريجابالين و هو مشتق من الناقل العصبي المثبط جابا لكنه على الرغم من ذلك لا يتحد مع مستقبلات جابا أو جابا ب ولا حتى مستقبلات البنزوديازيبين، كما إنه لا يتحول الى جابولا يؤثر على 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 التقليديه . وعلاوة على ذلك تم توسيع استخداماته العلاجيه مع مرور الوقت للسيطرة على الألام المزمنة وكذلك بعض حالات الألام الحاده . وهو دواء سهل الإستعمال وآمن وآثاره الجانبيه محدوده ، وأكثرها شيوعا الدوخة والنعاس.

و يصنف عقار الكلونيدين كإيميدازولين. و هو ناهض لمستقبلات ألفا ٢- و تأثيره الأساسى على مستقبلات ألفا- ٢ المركزيه ما قبل وبعد التشابك العصبى . و لعقار الكلونيدين نسبة انتقاء لمستقبلات ألفا٢- الى ألفا١- بنسبة ٢٠٠ الى ١. مدة العمر النصفى لعقار الكلونيدين هي ٨ ساعات، و هو متاح للإعطاء عن طريق الفم، عبر الجلد ، عن طريق العضل، فوق الأم الجافية، وعن طريق الوريد.

هذه الدراسه أجريت لمقارنه تأثير البريجابالين عن طريق الفم مقابل الكلونيدين عن طريق الفم ما قبل التخدير على رد الفعل الديناميكي للدوره الدمويه أثناء التنبيب الرغامى للمرضى الذين يجرون العمليات الجراحية البسيطة الإختيارية . قارنت أيضا الدراسه تأثيرهم على التهته المحيطة بالجراحة.

وقد أجريت الدراسه على ٤٠ مريض ينتمون إلى المستوى الأول أو الثاني في تصنيف الجمعية الأمريكية للتخدير أعمارهم تتراوح بين ١٨ و ٤٥ سنة من الجنسين . وقد تم استبعاد المرضى المصابين:

(بأمراض فى القلب والأوعيه الدمويه ، اختلال وظائف الكبد والكلى ، المصابون بالسمنة المفرطة ، مدمني الكحول أو الأدوية، من لديهم دلائل على صعوبة التنبيب أو يأخذون أدويه لمعالجة ارتفاع ضغط الدم والإكتئاب.) حيث تم عمل تقييم ما قبل العملية لجميع المرضى من خلال أخذ تاريخ مرضى مفصل، فحص إكلينيكي كامل، تقييم للممرات الهوائية و الفحوص المختبرية الروتينية.

وتم تقسيمهم عشوائيا باستخدام تقنية الظرف المغلق إلى مجموعتين متساويتين :

المجموعة الأولى: تم اعطاء المرضى قرص بريباجالين ١٥٠ ملجرام ٩٠ دقيقة قبل ادخال التخدير.

المجموعة الثانية: تم اعطاء المرضى قرص كلونيدين ٠,٢ ملجرام ٩٠ دقيقة قبل ادخال التخدير.

وقبل اعطاء المرضى الأقراص قد تم تسجيل مؤشراتهم الحيويه من ضغط الدم ،نبضات القلب ، تشبع الدم بالأوكسجين . ثم بعد دخولهم غرفة العمليات تم توصيلهم بجهاز قياس المؤشرات الحيويه واخذ قياسات.

وقد خضع جميع المرضى لنفس بروتوكول التخدير كالتالي:-

بدأ التخدير الكلى بإعطاء عقار الفنتانيل بجرعة ١ ميكروجم/كجم عقار البروبوفول ١٪ بجرعة ٢ ملجم /كجم تليها جرعة ٢,٠ ملجم /كجم من عقار السيزأتراكويريم عن طريق الوريد لتسهيل القيام بالتنبيب القصبة الهوائية ثم تم التنبيب في أقل وقت ممكن يتشابه في جميع المرضى وقد تم المحافظة على استمرار التخدير الكلى باستخدام عقار الأيزوفلورين ١-١,٥٪ في أوكسجين بنسبة ١٠٠٪ مع إعطاء جرعات إضافية من عقار السيزأتراكويريم بجرعة ٢,٠ ملجم /كجم كل نصف ساعة حتى انتهاء العملية.

القياسات:

- ١- البيانات الديمغرافية: وتشمل العمر والجنس
- ٢- معدلات الدورة الدموية: وتشمل معدل ضربات القلب، متوسط ضغط الدم الشرياني، وتشبع الأوكسجين الشرياني والتي تم قياسها قبل اعطاء الأقراس وقيل وبعده التخدير، بعد التنبيب، كل دقيقتين حتى مرور ١٠ دقائق، كل ١٥ دقيقة حتى نهاية العملية.

نتائج الدراسة :

في هذه الدراسة فيما يتعلق بالسن والجنس لا يوجد فرق كبير بين المجموعتين . أما فيما يتعلق بمعدل نبضات القلب وضغط الدم الشرياني فإن المجموعتين سجلتا انخفاض ملحوظ في هذين المؤشرين في جميع القياسات المأخوذة لكن حدث ارتفاع طفيف عند وقت دقيقتين (أكثر وقت ترتفع فيه المؤشرات الحيوية استجابة للتنبيب) ولكن الارتفاع لم يصل إلى القيمة الأولية وظل الانخفاض عنها واضح. ولكن الكلوئيد أفضل من البريجابالين.

أما فيما يتعلق بمستوى السكون: فقد قام العقارين تهدئة المرضى بشكل ملحوظ ولكن البريجابالين كان أفضل من الكلوئيد.

في ضوء النتيجة السابقة يمكن أن نستنتج الآتي:

- ١- وقد وجد أن اعطاء ٢,٠ ملليجرام من الكلوئيد أو ١٥٠ ملليجرام من البريجابالين عن طريق الفم قبل التخدير في المرضى الذين ينتمون إلى المستوى الأول أو الثاني في تصنيف الجمعية الأمريكية للتخدير يعتبر طريقة آمنة وفعالة نسبياً للحماية من الآثار الناتجة عن التنبيب.
- ٢- الكلوئيد أفضل من البريجابالين في تقليل ارتفاع الضغط وتسارع ضربات القلب الناتج عن التنبيب.
- ٣- البريجابالين أفضل من الكلوئيد في تهدئة المرضى .

في ضوء النتيجة السابقة يمكن أن نوصي بالآتي :

- ١- يمكن اعطاء ٢,٠ ملليجرام من الكلوئيد أو ١٥٠ ملليجرام بريجبالين عن طريق الفم على النحو الموصى به لجميع المرضى ذوي حالة صحية جيدة.
- ٢- ويلزم إجراء مزيد من الدراسات لمعرفة فعاليته في المرضى كبار السن والمرضى الذين ينتمون إلى المستوى الثالث أو الرابع في تصنيف الجمعية الأمريكية للتخدير خاصة في وجود خطورة على القلب والأوعية الدموية.
- ٣- الحاجة لمزيد من الدراسات الطبية للتعرف على دور هذين العقارين في تسكين الألم .
- ٤- المزيد من الدراسات للتعرف على ما إذا كان هناك آثار جانبية لهذين العقارين بعد العملية.



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رسالة مقدمة

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ضمن متطلبات درجة

الماجستير

فى

التخدير والعناية المركزة الجراحية

من

ولاء محمد مبروك زيدان
بكالوريوس الطب والجراحة ، ٢٠٠٨
كلية الطب، جامعة الإسكندرية

[٢٠١٥]



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رسالة مقدمة من

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للحصول على درجة

الماجستير

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التخدير والعناية المركزة الجراحية

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