

**P2X3 Receptor Expression in Dorsal Horn of Spinal Cord and Pain Threshold after
Estrogen Therapy for Prevention Therapy in Neuropathic Pain**

From: Rohadi Muhammad Rosyidi, MD, Neurosurgeon
Medical Faculty - Mataram University / General Proviencie West Nusa Tenggara Hospitals
Country : Indonesia

Date: November, 01, 2020

To,
Riaz Agha
Editor-in-Chief
Annals of Medicine and Surgery

Sub: Submission of manuscript for publication as a research article.

Dear Editor,

I, ABC, on behalf of my co-authors submit the following manuscript for publication consideration. I understand the objectives of the journal and have formatted the manuscript to fit the style and needs of the journal. **This manuscript is in accordance with the Authorship statement of ethical standards for manuscripts submitted to Annals of Medicine and Surgery.** I confirm that the manuscript has been prepared for and sent only to Journal of Annals of Medicine and Surgery for publication consideration and not submitted to any other journal or any other type of publication either by me or any of my co-authors.

**Title of the Article: “P2X3 Receptor Expression in Dorsal Horn of Spinal Cord and Pain
Threshold after Estrogen Therapy for Prevention Therapy in Neuropathic Pain ”**

Type of Article: Research

Author Name and Affiliation (In sequence):

Author order	Author Name (First name, Middle name initial followed by Family name)	Affiliation (Department, Institution, City, State, Country)
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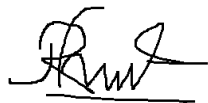
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2	Bambang Priyanto	Department of Neurosurgery Medical Faculty of Mataram University, West Nusa Tenggara General Hospital, Mataram Indonesia
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4	Krisna Tsaniadi Prihastomo	Department of Neurosurgery, Dr. Kariadi General Hospital Medical Center, Semarang, Center Java, Indonesia
5	Syauq Hikmi	Department of Neurosurgery, Dr. R. Koesma General Hospital Medical Center, Tuban, East Java, Indonesia
6	Agus Turchan	Department of Neurosurgery, Dr. Soetomo General Hospital Medical Center, Surabaya, East Java, Indonesia
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Dr. Rohadi Muhammad Rosyidi	Email: rha.ns2010@gmail.com	Contact No.: +628179714624 Address: Bangil V Street, No.1 BTN Taman Baru Pagesangan, Mataram City Lombok Island West Nusa Tenggara-Indonesia
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Thanking you,

Yours' sincerely,



Rohadi M. Rosyidi

Annals of Medicine and Surgery

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Please state any conflicts of interest

All authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

The authors declare that they have no conflict of interests

Please state any sources of funding for your research

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No funding or sponsorship

Ethical Approval

Research studies involving patients require ethical approval. Please state whether approval has been given, name the relevant ethics committee and the state the reference number for their judgement.

All procedure for Animal experiment has been approved by Animal Care and Use Committee (ACUC) Faculty of Veterinary Medicine, Airlangga University, Number: 236-KE.

Consent

Studies on patients or volunteers require ethics committee approval and fully informed written consent which should be documented in the paper.

Authors must obtain written and signed consent to publish a case report from the patient (or, where applicable, the patient's guardian or next of kin) prior to submission. We ask Authors to confirm as part of the submission process that such consent has been obtained, and the manuscript must include a statement to this effect in a consent section at the end of the manuscript, as follows: "Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request".

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This manuscript does not involve human participants, human data, or human tissue

Author contribution

Please specify the contribution of each author to the paper, e.g. study concept or design, data collection, data analysis or interpretation, writing the paper, others, who have contributed in other ways should be listed as contributors.

RHA, BAM, NUW, NAA, UQI and AGT wrote the manuscript and participated in the study design. RHA, BAM, NUW, NAA, UQI and AGT drafted and revised the manuscript. RHA, NUW, NAA, and UQI performed head trauma treatment and surgery. RHA, NAA, UQI and RZ performed bioinformatics analyses and revised the manuscript. All authors read and approved the final manuscript

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<ol style="list-style-type: none">1. Name of the registry:2. Unique Identifying number or registration ID:3. Hyperlink to your specific registration (must be publicly accessible and will be checked): <p>None</p>
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Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish

Rohadi Muhammad Rosyidi

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<em@editorialmanager.com>

Fri, Aug 21, 2020, 10:59
AM

to me

Dear Dr Rosyidi,

Thank you for sending your manuscript P2X3 Receptor Expression in Dorsal Horn of Spinal Cord and Pain Threshold after Estrogen Therapy for Prevention in Neuropathic Pain for consideration to Annals of Medicine and Surgery. Please accept this message as confirmation of your submission. When should I expect to receive the Editor's decision?

For Annals of Medicine and Surgery, the average editorial time (in weeks) from submission to first decision is: 5.07 and from submission to final decision is: 10.13.

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2. If your manuscript matches the scope and satisfies the criteria of Annals of Medicine and Surgery, the Editor will identify and contact reviewers who are acknowledged experts in the field. Since peer-review is a voluntary service, it can take some time but please be assured that the Editor will regularly remind reviewers if they do not reply in a timely manner. During this stage, the status will appear as "Under Review".

Once the Editor has received the minimum number of expert reviews, the status will change to "Required Reviews Complete".

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Dr. Riaz Agha

Editor-in-Chief

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Fri, Oct 30, 2020,
8:57 AM

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Journal: Annals of Medicine and Surgery

Ref: AMSU-D-20-00375

Title: P2X3 Receptor Expression in Dorsal Horn of Spinal Cord and Pain Threshold after Estrogen Therapy for Prevention in Neuropathic Pain

Dear Dr Rosyidi

I am pleased to inform you that the status of your submission has now progressed to: 'Required reviews complete'.

This status means that I have received the minimum number of required reviews, which I will now evaluate in order to make a decision on your paper.

If the current reviews conflict with one another or are not detailed enough, I may need to seek the opinion of another reviewer to make a fair and informed conclusion about your paper. For this reason the status of your paper may change back to 'under review' for a short period of

time.

As soon as the final editor's decision can be made, you will be notified via email.

I appreciate your understanding of the time required to provide you with a thorough decision and comments on your submission.

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Ms. Ref. No.: AMSU-D-20-00375R1

Title: P2X3 Receptor Expression in Dorsal Horn of Spinal Cord and Pain Threshold after Estrogen Therapy for Prevention in Neuropathic Pain
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Respon to Reviewer

Reviewers' comments:

Reviewer #5: - Is it possible to clarify why hyperalgesia was performed 30 minutes post-injection? ('effect of estrogen application...' subsection)

Answer :

Thanks Sir. I've added it to the subsection

“Allodynia (pain due to a stimulus that does not usually provoke pain) and hyperalgesia (increased pain from a stimulus that usually provokes pain) are prominent symptoms in patients with neuropathic pain. Neuropathic pain causes signs and symptoms of hyperalgesia, so to understand the inhibition of neuropathic pain in each drug, the measurement of hyperalgesia is performed. Measurement of hyperalgesia on days 1, 3, 5, 7, and 14 using a warm plate. Measurement of hyperalgesia was done 30 minutes post-injection, each injection and measurement of hyperalgesia were completed per group. It is intended that each group has the same interval between subcutaneous injection with hyperalgesia measurement and 30 minutes is the average drug can reach peak effect so that it can be seen the pain reduction response between the positive control group and the estrogen group”

- Are there any alternative and equally as effective forms of treatment for neuropathic pain?

Answer :

Thanks Sir. I've added it to the discussion

“Numerous therapeutic and Prevent recommendations, with different classes of drug, for neuropathic pain have been proposed. On the basis of a systematic review and meta-analysis of all drug studies reported on since 1966, including unpublished trials, pregabalin (a GABA analogue), gabapentin (a GABA inhibitor), duloxetine (a serotonin-noradrenaline reuptake inhibitor) and various tricyclic antidepressants have strong recommendations for use and are recommended as first-line treatments for peripheral and central neuropathic pain. High-concentration capsaicin (the active component of chili peppers) patches, lidocaine patches and tramadol (an opioid with serotonin and noradrenaline reuptake inhibition effects) have weak evidence in support of their use and are recommended as second-line treatments for peripheral neuropathic pain only. Strong opioids and botulinum toxin A (administered by specialists) have weak recommendations for use as third-line treatments. However, most of these treatments have moderate efficacy based on the number needed to treat for obtaining

50% of pain relief. Furthermore, pharmacological treatments for chronic neuropathic pain are effective in <50% of patients and may be associated with adverse effects that limit their clinical utility. It is because of the much dissatisfaction with the therapy that many studies have been conducted to find the right remedy for neuropathic pain. It is on this basis that we conducted research on one of the drugs, namely estrogen. We looked at how the estrogen effects to prevent neuropathic pain.

Estrogens are reported to reduce the sensation of pain and estrogen acting on beta receptors can provide protection from pain due to inflammation. In neuropathic pain, estrogen can modulate pain via both peripheral and central routes. In the peripheral nerves, especially in the dorsal horn of the spinal cord and DRG (dorsal root ganglia) through non-genomic, genomic, and paracrine regulation. Estrogen plays a role in the survival and regeneration of spinal neurons. In DRG neurons and spinal horn dorsal horn, estrogen reduces the entry of Ca²⁺ ions triggered by ATP via α estrogen receptors and selectively acts to modulate impulses mediated by P2X₃ receptors. Centrally, estrogen triggers neurochemical changes that can modulate pain.”

- If would be helpful if the authors included in the discussion/conclusion what the key take away messages of this report are, and what has been learnt.

Answer :

Thanks Sir. I've added it to the discussion.

“From this study, it was found how the role of estrogen can prevent neuropathic pain, where is estrogen could decrease the expression of P2X₃ receptors and prolonged the onset of thermal hyperalgesia. So, both of these explained that estrogen has a role in preventing the occurrence of neuropathic pain after peripheral nerve lesions”.

- Please discuss the limitations and challenges encountered throughout this study, and how they were effectively overcome.

Answer :

Thanks Sir. I've added it to the discussion

“The limitation of this study is that the research was carried out on experimental animals so that it needs to be continued in the future with clinical research involving others biomarkers for neuropathic pain ”

Submission Confirmation for AMSU-D-20-00375R1 Inbox x



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Sun, Nov 1, 2020, 1:03 PM

to me

Ms. Ref. No.: AMSU-D-20-00375R1

Title: **P2X3 Receptor Expression in Dorsal Horn of Spinal Cord and Pain Threshold after Estrogen Therapy for Prevention in Neuropathic Pain**
Annals of Medicine and Surgery

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Title: **P2X3 Receptor Expression in Dorsal Horn of Spinal Cord and Pain Threshold after Estrogen Therapy for Prevention in Neuropathic Pain**
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Sun, Nov 1, 2020, 1:03
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to me

Ms. Ref. No.: AMSU-D-20-00375R1

Title: P2X3 Receptor Expression in Dorsal Horn of Spinal Cord and Pain Threshold
after Estrogen Therapy for Prevention in Neuropathic Pain
Annals of Medicine and Surgery

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Title: P2X3 Receptor Expression in Dorsal Horn of Spinal Cord and Pain Threshold
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Annals of Medicine and Surgery

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Sun, Nov 1, 2020, 10:47
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to me

Ms. Ref. No.: AMSU-D-20-00375R1

Title: P2X3 Receptor Expression in Dorsal Horn of Spinal Cord and Pain Threshold
after Estrogen Therapy for Prevention in Neuropathic Pain
Annals of Medicine and Surgery

Dear Dr Rosyidi,

Your submission "P2X3 Receptor Expression in Dorsal Horn of Spinal Cord and Pain Threshold
after Estrogen Therapy for Prevention in Neuropathic Pain" will be handled by Editor in Chief
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Mon, Nov 2, 2020, 2:50
AM

to me

Ms. Ref. No.: AMSU-D-20-00375R1

Title: P2X3 Receptor Expression in Dorsal Horn of Spinal Cord and Pain Threshold after Estrogen Therapy for Prevention in Neuropathic Pain
Annals of Medicine and Surgery

Dear Dr Rosyidi,

I am pleased to inform you that your paper "P2X3 Receptor Expression in Dorsal Horn of Spinal Cord and Pain Threshold after Estrogen Therapy for Prevention in Neuropathic Pain" has been accepted for publication in Annals of Medicine and Surgery.

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Thank you for submitting your work to Annals of Medicine and Surgery.

Yours sincerely,

Jo Frankland
Editorial Office
Annals of Medicine and Surgery

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Article title: P2X3 Receptor Expression in Dorsal Horn of Spinal Cord and Pain Threshold after Estrogen Therapy for Prevention in Neuropathic Pain

Reference: AMSU1924

Journal title: Annals of Medicine and Surgery

Corresponding author: Dr Rohadi Muhammad Rosyidi

First author: Dr. Rohadi Muhammad Rosyidi

Dear Dr Rosyidi,

Your article P2X3 Receptor Expression in Dorsal Horn of Spinal Cord and Pain Threshold after Estrogen Therapy for Prevention in Neuropathic Pain will be published in Annals of Medicine and Surgery.

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Title: P2X3 Receptor Expression in Dorsal Horn of Spinal Cord and Pain Threshold after Estrogen Therapy for Prevention in Neuropathic Pain
Annals of Medicine and Surgery

Dear Dr Rosyidi,

I am pleased to inform you that your paper "P2X3 Receptor Expression in Dorsal Horn of Spinal Cord and Pain Threshold after Estrogen Therapy for Prevention in Neuropathic Pain" has been accepted for publication in Annals of Medicine and Surgery.

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Submissions with an Editorial Office Decision for Author Rohadi Muhammad Rosyidi, MD; Neurosurgeon

Page: 1 of 1 (6 total completed submissions)

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Action	Manuscript Number	Title	Initial Date Submitted	Status Date	Current Status	Date Final Disposition Set	Final Disposition
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