Chronic migraine patients have low level of knowledge about pain neurophysiology

Pacientes com migrânea crônica apresentam baixo nível de conhecimento sobre neurofisiologia da dor

Maria Ivone Oliveira Dantas¹, Thaís Alves Barreto Pereira², Josimari Melo DeSantana^{1,2}

DOI 10.5935/2595-0118.20210064

ABSTRACT

BACKGROUND AND OBJECTIVES: Identify the level of knowledge about the neurophysiology of pain in patients with chronic migraine through the application of the Neurophysiology of Pain Questionnaire.

METHODS: A cross-sectional study was carried out with 30 patients with chronic migraine. The level of neurophysiological knowledge of pain was assessed by the Brazilian version of the Neurophysiology of Pain Questionnaire.

RESULTS: In general, patients with chronic migraine had a low level of knowledge about pain neurophysiology with 4.03 ± 1.52 correct answers in 12 questions (34.1%). From those 30 patients, there was a predominance of females (72.7%), aged 33 ± 8.60 years, higher schooling level (73.4%), mild intensity of pain at rest (2.83±2.39), predominant subclassification of chronic migraine without aura (56.7%) and with a history of migraine for more than 10 years (60.1%). This article identified the level of knowledge about neurophysiology of pain in chronic migraines through the application of the Neurophysiology of Pain Questionnaire.

CONCLUSION: Patients with chronic migraine have a low level of neurophysiological knowledge.

Keywords: Chronic pain, Migraine disorders, Neurophysiology, Pain management.

Maria Ivone Oliveira Dantas – ©https://orcid.org/0000-0002-5948-4797; Thaís Alves Barreto Pereira – ©https://orcid.org/0000-0003-3833-3161; Josimari Melo DeSantana – ©https://orcid.org/0000-0003-1432-0737.

2. Federal University of Sergipe, Health Sciences Graduate Program, São Cristóvão, SE, Brasil.

Submitted on April 18, 2021. Accepted for publication on September 17, 2021. Conflict of interests: none – Sponsoring sources: none.

Correspondence to: E-mail: desantanajm@gmail.com

© Sociedade Brasileira para o Estudo da Dor

RESUMO

JUSTIFICATIVA E OBJETIVOS: Identificar o nível de conhecimento sobre a neurofisiologia da dor na migrânea crônica por meio da aplicação do Questionário de Neurofisiologia da Dor.

MÉTODOS: Foi realizado um estudo transversal com 30 pacientes com migrânea crônica. O nível de conhecimento neurofisiológico da dor foi avaliado pela versão brasileira do Questionário de Neurofisiologia da Dor.

RESULTADOS: Em geral, pacientes com migrânea crônica apresentaram baixo nível de conhecimento sobre a neurofisiologia da dor com 4,03 \pm 1,52 acertos em 12 questões (34,1%). Destes 30 pacientes, houve predomínio do sexo feminino (72,7%), idade 33 \pm 8,60 anos, maior escolaridade (73,4%), intensidade de dor leve em repouso (2,83 \pm 2,39), subclassificação predominante de migrânea crônica sem aura (56,7%) e com história de migrânea há mais de 10 anos (60,1%). Este artigo identificou o nível de conhecimento sobre a neurofisiologia da dor na migrânea crônica por meio da aplicação do Questionário de Neurofisiologia da Dor.

CONCLUSÃO: Pacientes com migrânea crônica apresentam baixo nível de conhecimento neurofisiológico.

Descritores: Dor crônica, Manejo da dor, Neurofisiologia, Transtornos de migrânea.

INTRODUCTION

Pain is the main symptom mentioned in health centers, considered a global problem, and affecting a large part of the world population at some point in life¹. Evidence from the Global Burden of Disease Survey², a study that covered a 28-year period, showed that three chronic non-communicable diseases, namely, low back pain, headache and depressive disorders, currently prevail as the main causes of years lived with disabilities².

Migraine is a disorder that presents a pulsating, unilateral character, which may or may not be accompanied by nausea, vomiting, phonophobia, photophobia and osmophobia³. Primary chronic migraine does not have a known causative factor, however, it's currently considered the first cause of disability in individuals under 50 years of age⁴, and has a high socioeconomic burden⁵. In Brazil, migraine is the second most common noncommunicable disease and the most disabling, affecting occupational, academic, social, family and personal domains of affected individuals⁶⁻⁹.

^{1.} Federal University of Sergipe, Physiological Sciences Graduate Program, São Cristóvão, SE, Brazil.

Lack of knowledge can also affect people's ability to control their painful characteristics, especially when it comes to chronic pain¹⁰. Consequently, alternative interventions that improve this understanding of the public can reduce their stigmas, whether through awareness campaigns or monitoring the advertising of painkillers and, consequently, reducing the years lived with disability⁸.

Neuroscience-based pain education (PNE, Pain Neuroscience Education) is an alternative strategy for contributing to the management of painful conditions, following in its principles the foundations of educational psychology, which aims to "reconceptualize pain", through the acquisition of knowledge about neurophysiological, biological and social mechanisms of pain, demystifying patient's beliefs and fears^{11,12}.

Evidence demonstrates, through the use of PNE, that patients with chronic low back pain¹³, fibromyalgia and/or chronic fatigue syndrome^{14,15}, and general chronic pain^{10,16} show better patient satisfaction, greater adherence to other therapies, improved function and decreased catastrophization and kinesiophobia.

Neurophysiology of Pain Questionnaire (NPQ) is self-administered, widely used to assess the level of knowledge about neurophysiological and biological mechanisms involved in pain, in different populations, whether professionals or patients^{11,12}. Previous studies have assessed the level of knowledge through the NPQ in physical therapy students^{17,18}, students in the health sciences¹⁹, and patients with fibromyalgia²⁰ and chronic musculoskeletal pain^{14,21}.

Chronic migraine patients are often underdiagnosed and undertreated in healthcare systems⁴. The perception of health conditions has already been considered as an option in the development of therapeutic plans, with that the importance of demystifying beliefs and providing knowledge to patients about the etiological factors of the disease, associated symptoms and forms of management is noted.

Most migraine patients do not understand how severe and disabling their condition may be, and consequently, they do not develop adequate self-management, hence the importance of assessing the knowledge of these individuals. Therefore, the objective of this article was to identify the level of knowledge about neurophysiology of pain in chronic migraines through the application of the NPQ.

METHODS

Epidemiological, observational, cross-sectional study whose target population consisted of patients aged 18 to 55 years old with a diagnosis of chronic migraine headache, following the diagnostic criteria of the International Society for the Study of Headaches (Table 1). This diagnosis was made by a neurologist at the University Hospital of the Federal University of Sergipe (HU-UFS), a specialist in headache care and was not involved in the study. Patients were excluded from the study if they had other types of associated secondary headaches, neurological or psychiatric diseases, inability to understand the instructions or consent to the study, severe respiratory diseases, history of head and neck trauma, and comorbidities with headache symptoms, such as high blood pressure and fibromyalgia.

Participants completed an evaluation form consisting of demographic data such as age, height, weight, body mass index (BMI),
 Table 1. The International Classification of Headache Disorders

 (ICHD-3) diagnostic criteria for primary headache disorders

- 1. Headache (migraine-type or tension-type) at \geq 15 days/month for >3 months meeting criteria 2 and 3.
- Attacks occur in an individual who has had at least five attacks that meet criteria for no aura migraine and/or migraine with aura.
- 3. At \geq 8 days/month for >3 months, any of the following criteria is met:
 - criteria 3 and 4 for migraine without aura
 - criteria 2 and 3 for migraine with aura
 - that the patient believes to be migraine at first and relieved by a triptan or ergot derivative
- 4. Not better explained by another diagnosis of ICDH-3.

Source: The International Classification of Headache Disorders (2018)

age when the migraine attacks started happening, history of current illness, triggers for attacks, premonitory symptoms, family history, drugs used, associated diseases and social history. The level of knowledge about pain neurophysiology was assessed by using the Brazilian version of the NPQ²⁴.

The NPQ was designed to assess how the individual conceptualizes the biological mechanisms involved in pain¹². Originally, its version has 19 items, with the following answer options: true, false, and undecided¹². However, the Brazilian version validated¹² presents 12 items, and the answer options also consist of "true, false or undecided". Its psychometric properties constitute a onedimensional scale with good test-retest reliability. The results are interpreted as follows: each hit corresponds to one point, if the individual makes a mistake or choose the "undecided" alternative, the item is reset to zero; therefore, the score ranges from zero to 12, and the higher the score, the greater the level of understanding of the mechanisms present in pain²⁴.

This questionnaire was chosen for the Brazilian 12-item version as it is self-applicable to address aspects in the assessment of basic neurophysiological knowledge of pain in people of all skill levels, regardless of basic schooling levels^{12,23}.

This study was approved by the Federal University of Sergipe Ethics Committee on Human Research (CAEE: 08310319.1.0000.5546). All subjects included in the study signed a Free and Informed Consent Term (FICT) prior to the evaluation, in compliance with the provisions of Resolution 466/12 of the National Health Council. The present study considered and served the requirements of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement, which provides subsidies for the communication of observational studies²².

Statistical analysis

The characteristics of the studied population were described as mean and standard deviation for the numerical variables and in absolute and percentage values for the category of categorical variables.

RESULTS

Initially, 65 volunteers were contacted through telephone screening from a waiting list, however 33 participants were excluded

Table 2.	Characteristics	of the	study	partici	pants
----------	-----------------	--------	-------	---------	-------

51	•			
Characteristics	Percentage (n=30)			
Gender Female Male	72.7 18.3			
Schooling level Basic level Graduate level	26.6 73.4			
Pain duration 3 months – 5 years 5 – 10 years > 10 years	16.6 23.3 60.1			
Subclassification Migraine without aura Migraine with aura	56.7 43.3			

Source: The author (2020). Data are presented as mean and standard deviation from the mean for continuous variables and as frequency count (%) for categorical variables.

Table 3. Percentage of correct answers to each question in the Neurophysiology of Pain Questionnaire offered by patients with chronic migraine

Item	True	False	Undecided
1. When you are injured, special re- ceptors convey the danger message to your spinal cord.	6.6	86.6	6.6
2. Pain only occurs when you are in- jured or at risk of being injured.	30	33.3	36.6
3. Special nerves in your spinal cord convey 'danger' messages to your brain.	70	3.3	26.6
4. Pain occurs whenever you are injured.	60	26.6	13.3
5. The brain decides when you will experience pain.	23.3	46.6	30
6. Nerves adapt by making ion chan- nels stay open longer.	43.3	16.6	40
7. Chronic pain means that an injury hasn't healed properly.	36.6	46.6	16.6
8. Worse injuries always result in worse pain.	36.6	33.3	30
9. Descending neurons are always inhibitory.	3.3	6.6	90
10. When you injure yourself, the environment that you are in will not affect the amount of pain you ex- perience, as long as the injury is exactly the same.	23.3	50	26.6
11. It is possible to have pain and not know about it.	33.3	43.3	23.3
12. When you are injured, special receptors convey the danger message to your spinal cord.	36.6	26.6	36.6

Data are presented as percentage.

because 20 did not meet the inclusion criteria, 3 gave up participating and 10 were excluded for other reasons. Therefore, 32 volunteers were recruited to this study. However, as two of them did not attend the evaluations, 30 volunteers were included.

From those 30 patients, there was a predominance of females (72.7%), aged 33 ± 8.60 years, higher education level (73.4%), intensity of mild pain at rest (2.83±2.39), predominant subclassification of chronic migraine without aura (56.7%) and with a history of migraine for more than 10 years (60.1%) (Table 2).

The main triggers mentioned by the patients were: stress (76.7%), menstrual cycle (63.3%), sleep disturbance (63.3%), lights/sounds (40%), fasting (36.7%), food (36.7%), temperature changes (33.3%), strong odors (30%) and physical effort (20%). The most common premonitory symptoms were changes in mood (40%), difficulties in concentration (40%), fatigue (36.7%), cervical sensitivity (30%) and hypo or hyperactivity (23.3%). The majority reported positive family history (78.6%), a portion performed regular physical activities (56.7%), small portion consumed alcohol socially (33.3%), a minority had already undergone some type of surgery (30%) and 43.3% had no associated diseases.

In general, patients with chronic migraine had a low level of knowledge about pain neurophysiology with 4.03±1.52 correct answers in 12 questions (34.1%). Table 3 shows the total of correct answers in each item of the NPQ.

DISCUSSION

The primary objective of this study was to investigate the level of knowledge about pain neurophysiology in chronic migraineurs. In general, chronic migraine patients exhibited a low level of knowledge, as measured by the NPQ in the 12-item version. In this study, the sample was composed predominantly of women, who had mild pain intensity at rest. Still, the main trigger identified was stress, and that mood changes and difficulties in concentration were the most prevalent premonitory symptoms and most patients had a positive family history.

The low level of knowledge about pain has already been evidenced in some groups of patients with clinical pain, such as low back pain¹⁴, chronic musculoskeletal pain²¹ and fibromyalgia²⁰, as well as health students¹⁹ and health professionals¹². Therefore, it is observed that there is a low level of knowledge, both in the groups of patients and in students and health professionals. In this context, there is a need to implement specific curricula on pain during graduation, aiming at better preparing these professionals to welcome and manage these pains in a multidisciplinary way.

The International Association for the Study of Pain has already developed a proposal for an interprofessional and intraprofessional pain curriculum for health care providers²⁴. In Brazil, current physical therapy and psychology courses have curricular guidelines for the study of pain^{25,26}. For patients, the implementation of these curricula in the graduation of professionals who will aid their painful conditions represents better management, consequently, this patient will suffer less and have their painful condition treated more adequately. It is also noteworthy that health professionals have an important role in this aspect, so their training needs to be minimally equipped with knowledge related to pain, aiming at better care and an integrative approach for these individuals, enabling the addition of education in their therapeutic plans, resulting in better patient adherence to treatment.

The cross-sectional study²¹ aimed at identifying the level of knowledge of the neurophysiology of pain in patients with chronic musculoskeletal pain and to compare the level of knowledge of pain according to the type of skeletal pain classification in the Brazilian population. In this study, it was observed that patients with chronic musculoskeletal pain got about 3.7 (out of 12) answers correctly using the NPQ, regardless of the pain classification based on its mechanism, thus corroborating the present study's findings, and evidencing a similarity between both patient populations.

With another approach, the study¹⁹ compared knowledge about pain in first- and last-year college students in the health area, including students of medicine, physical therapy, and nutrition. This study, unlike the present one, used the NPQ version with 19 questions to compare the number of correct answers in the questionnaire, the percentage of correct answers (score %) was calculated with the equation ([No. of correct answers / 19] × 100). The percentage values of correct answers in the first year, according to the courses, were 42.7±11.7 (physical therapy), 42.2±13.2 (medicine) and 41.3±10.1 (nutrition); for the last year, the students answered 68.9% (±16.2), 54.4% (±13.9) and 42.3% (±10.1) for physical therapy, medicine and nutrition, respectively.

With these results, it's possible to infer that the physical therapy course was the one that presented the most satisfactory knowledge during graduation, even though the authors concluded that the understanding may not be enough and still does not guarantee an approach to chronic pain that can help the patient to reconceptualize their pain¹⁹.

Although the participants included in this study had, for the most part, a higher schooling level, this did not imply the low level presented about basic knowledge in neurophysiology of pain. This may have occurred due to the attitudes and beliefs pre-established by this patient profile²⁷ or due to some cognitive decline, such as memory impairments²⁹. Given that chronic pain is considered multifactorial, there is a need for pain management in the context of social, biological, psychological and physical factors²⁹.

It should be noted that the item with the highest rate of correct answers was question 3, about the presence of special nerves in the spinal cord responsible for carrying pain messages to the brain. The greatest number of errors was present in item 1, referring to special pain receptors in the presence of injury to a part of the body. As for item 9, referring to the question about the inhibitory descending neurons, the participants were most undecided.

These items could easily be answered taking into account, for example, an approach according to Explain Pain^{11,12}, widely used in neuroscience-based education. In this work, in a simple way, the basic knowledge of pain biology is taught and,

thus, patients can develop the ability to modulate their own pain. The effect of PNE on other groups of chronic pain patients is already evident, such as fibromyalgia, chronic musculoskeletal pain and low back pain^{13,15}. Therefore, it is believed that the implementation of this strategy can also benefit patients with migraine.

Interestingly, a point that deserves attention is that these patients with migraine tend to self-medicate and consequently abuse analgesics, being considered as a factor associated with the process of chronic migraine. Eventually, the hypothesis was that education-based approaches could minimize this exacerbated use of drugs, helping to self-manage pain in these patients.

Additionally, the importance to evaluate and measure pain-related aspects should be highlighted. The evaluation of painful phenomena corresponds to the general magnitude of the experience reported by the patient in different situations, considering the physical, sensory, affective, and temporal dimensions. The present study used a self-report analysis that can supply one of the points related to the dimensions of pain studies and can be easily applied in clinical practice to guide treatment decisions.

It's important to emphasize that further studies need to be carried out to address this gap, bringing neuroscience-based education with an approach included in the multidisciplinary therapeutic plan in this patient population. This is the first study known by the authors to investigate the knowledge of the neurophysiology of pain in patients with chronic migraine.

Finally, some limitations of the study need to be mentioned, such as the low number of participants and the patient bias as a respondent through self-report, thus limiting the generalization of results. However, it is recommend that PNE strategies should be incorporated into the management of these patients through educational programs in future studies, as other groups of patients have already benefited from the incorporation of these interventions.

CONCLUSION

Patients with chronic migraine have a low level of neurophysiological knowledge.

ACKNOWLEDGMENTS

To the National Council for Scientific and Technological Development (CNPq), Coordination for the Improvement of Higher Education (Capes) and Foundation for Research and Technological Innovation of Sergipe State (FAPITEC/SE) for the help of cost and the entire Functional Training Group for their contribution in data collection.

AUTHORS' CONTRIBUTIONS

Maria Ivone Oliveira Dantas

Statistical analysis, Data Collection, Resource Management, Project Management, Research, Methodology, Writing - Preparation of the original, Writing - Review and Editing, Supervision, Visualization

Thaís Alves Barreto Pereira

Data Collection, Conceptualization, Resource Management, Project Management, Research, Methodology, Writing - Review and Editing

Josimari Melo DeSantana

Funding Acquisition, Conceptualization, Resource Management, Project Management, Research, Methodology, Writing - Preparation of the original, Writing - Review and Editing, Supervision, Visualization

REFERENCES

- Hudspith MJ. Anatomy, physiology and pharmacology of pain. Anaesth Intens Care Med. 2016;17(9):425-30.
- GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1545-602.
- ICHD-3-Brazilian-Portuguese-translation-25062019.pdf. Accessed November 28, 2020. https://ichd-3.org/wp-content/uploads/2019/06/ICHD-3-Brazilian-Portuguese-translation-25062019.pdf
- Steiner TJ, Stovner LJ, Vos T, Jensen R, Katsarava Z. Migraine is first cause of disability in under 50s: will health politicians now take notice? J Headache Pain. 2018;19(1):17.
- Leonardi M, Raggi A. A narrative review on the burden of migraine: when the burden is the impact on people's life. J Headache Pain. 2019;20(1):41.
- Malta DC, Bernal RTI, Lima MG, Araújo SSC, Silva MMAD, Freitas MIF, et al. Noncommunicable diseases and the use of health services: analysis of the National Health Survey in Brazil. Rev Saúde Pública. 2017;51(Suppl1):4s.
- Malta DC, Stopa SR, Szwarcwald CL, Gomes NL, Silva Júnior JB, Reis AAC. A vigilância e o monitoramento das principais doenças crônicas não transmissíveis no Brasil - Pesquisa Nacional de Saúde, 2013. Rev Bras Epidemiol. 2015;18(Suppl 2):3-16.
- Peres MFP, Oliveira AB, Sarmento EM, Rocha-Filho PS, Peixoto PM, Kowacs F, et al. Public policies in headache disorders: needs and possibilities. Arqu Neuropsiquiatr. 2020;78(1):50-2.
- Peres MFP, Queiroz LP, Rocha-Filho PS, Sarmento EM, Katsarava Z, Steiner TJ. Migraine: a major debilitating chronic non-communicable disease in Brazil, evidence from two national surveys. J Headache Pain. 2019;20(1):85.
- King R, Robinson V, Ryan CG, Martin DJ. An exploration of the extent and nature of reconceptualisation of pain following pain neurophysiology education: a qualitative study of experiences of people with chronic musculoskeletal pain. Patient Educ Couns. 2016;99(8):1389-93.
- Moseley GL, Butler DS. Fifteen years of explaining pain: the past, present, and future. J Pain. 2015;16(9):807-13.
- 12. Moseley L. Unraveling the barriers to reconceptualization of the problem in chronic

pain: the actual and perceived ability of patients and health professionals to understand the neurophysiology. J Pain. 2003;4(4):184-9.

- Wood L, Hendrick PA. A systematic review and meta-analysis of pain neuroscience education for chronic low back pain: short-and long-term outcomes of pain and disability. Eur J Pain. 2019;23(2):234-49.
- Louw A, Zimney K, Puentedura EJ, Diener I. The efficacy of pain neuroscience education on musculoskeletal pain: A systematic review of the literature. Physiother Theory Pract. 2016;32(5):332-55.
- van Ittersum MW, van Wilgen CP, van der Schans CP, Lambrecht L, Groothoff JW, Nijs J. Written pain neuroscience education in fibromyalgia: a multicenter randomized controlled trial. Pain Pract. 2014;14(8):689-700.
- Robinson V, King R, Ryan CG, Martin DJ. A qualitative exploration of people's experiences of pain neurophysiological education for chronic pain: the importance of relevance for the individual. Man Ther. 2016;22:56-61.
- Bareiss SK, Nare L, McBee K. Evaluation of pain knowledge and attitudes and beliefs from a pre-licensure physical therapy curriculum and a stand-alone pain elective. BMC Med Educ. 2019;19(1):375.
- Springer S, Gleicher H, Hababou H. Attitudes and beliefs about musculoskeletal pain and its association with pain neuroscience knowledge among physiotherapy students in Israel. Isr J Health Policy Res. 2018;7(1):67.
- Adillón C, Lozano È, Salvat I. Comparison of pain neurophysiology knowledge among health sciences students: a cross-sectional study. BMC Res Notes. 2015;8:592.
- Amer-Cuenca JJ, Pecos-Martín D, Martínez-Merinero P, Lluch Girbés E, Nijs J, Meeus M, et al. How much is needed? Comparison of the effectiveness of different pain education dosages in patients with fibromyalgia. Pain Med. 2020;21(4):782-93.
- Ferreira PS, Corrêa LA, Bittencourt JV, Reis FJJ, Meziat-Filho N, Nogueira LAC. Patients with chronic musculoskeletal pain present low level of the knowledge about the neurophysiology of pain. Eur J Physiother. 2021;23(4):1-6.
- Malta M, Cardoso LO, Bastos FI, Magnanini MMF, Silva CMFP da. Iniciativa STROBE: subsídios para a comunicação de estudos observacionais. Rev Saúde Pública. 2010;44(3):559-65.
- Nogueira LAC, Chaves AO, Oliveira N, Almeida RS, Reis JJR, Andrade FG, et al. Cross-cultural adaptation of the Revised Neurophysiology of Pain Questionnaire into Brazilian Portuguese language. J Bras Psiquiatr. 2018;68(4):273-7.
- Watt-Watson J, Davies R, Langlois S, Oskarsson J, Raman-Wilms L. The pain interprofessional curriculum design model. Pain Med. 2017;18(6):1040-8.
- DeSantana JM, Souza JB, Reis FJ, Goslind AP, Paranhos E, Barbosa HF, et al. Pain curriculum for graduation in Physiotherapy in Brazil. Rev Dor. 2017;18(1):72-8.
- Sardá Junior JJ, Perissinotti DM, Ros MÁ, Siqueira JL. Pain curricular guidelines for Psychologists in Brazil. BrJP. 2019;2(1):61-6.
- Matsuzawa Y, Lee YSC, Fraser F, Langenbahn D, Shallcross, Powers S, et al. Barriers to behavioral treatment adherence for headache: an examination of attitudes, beliefs, and psychiatric factors. Headache. 2019;59(1):19-31,
- Chu HT, Liang CS, Lee JT, Sung YF, Tsai CL, Tsai CK, et al. Subjective cognitive complaints and migraine characteristics: A cross-sectional study. Acta Neurol Scand. 2020;141(4):319-27.
- Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. Br J Anaesth. 2019;123(2):e273-e283.