

Laboratory animals and analgesia: the responsibility of ethics committees and the obligations of researchers

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Abstract

The aim of the present study was to evaluate projects submitted to an Animal Research Ethics Committee regarding the use of analgesia in experimental surgery. A total of 106 projects submitted to the Animal Research Ethics Committee were evaluated and the following information was collected: methodology of the surgical procedure, use of analgesia, justification of the non-use of analgesia and application of the degree of invasiveness. Of the projects evaluated, 64.2% used surgical techniques, of which 65.6% did not use analgesia postoperatively, with the main reason being that the analgesic could alter the results. In 17% of cases the classification of the degree of invasiveness was used in an irregular manner. The stimulation and dissemination of analgesia-related knowledge must stem from both the ethics committees responsible and researchers.

Keywords: Bioethics. Laboratory animals. Experimental surgery.

Resumo

Analgésia de animais de laboratório: responsabilidade dos comitês de ética e obrigação dos pesquisadores

Objetivando avaliar projetos submetidos ao Comitê de Ética no Uso de Animais em relação ao uso de analgesia em cirurgia experimental de animais, este trabalho avaliou 106 projetos, coletando as seguintes informações: metodologia do procedimento cirúrgico, utilização de analgesia, justificativa do não uso de analgésico e aplicação do grau de invasividade. Dos projetos avaliados, 64,2% empregaram técnica cirúrgica. Destes, 65,6% não utilizaram analgesia no pós-operatório, sendo a principal justificativa a de que o analgésico poderia alterar os resultados; em 17%, empregou-se a classificação de grau de invasividade de forma irregular. Assim, o estímulo e a divulgação dos conhecimentos relacionados a analgesia devem partir tanto dos comitês responsáveis quanto do corpo de pesquisadores.

Palavras-chave: Bioética. Animais de laboratório. Cirurgia experimental.

Resumen

Analgésia de animales de laboratorio: responsabilidad de los comités de ética y obligación de los investigadores

Con el objetivo de evaluar los proyectos presentados al Comité de Ética en el Uso de Animales con respecto al uso de la analgesia en cirugía experimental, este estudio evaluó 106 proyectos y obtuvo la siguiente información: la metodología de la intervención quirúrgica, el uso de la analgesia, la justificación de no utilizar analgésico y la aplicación del grado de invasividad. De los proyectos evaluados, un 64,2% empleó técnicas quirúrgicas, de los cuales un 65,6% no utilizó analgesia en el postoperatorio, justificando principalmente que el analgésico podría alterar los resultados, y en un 17% la clasificación del grado de invasividad se utilizó de manera irregular, por lo que la estimulación y la difusión de los conocimientos relacionados con la analgesia deben partir tanto de los comités responsables como del cuerpo de investigadores.

Palabras clave: Bioética. Animales de laboratorio. Cirugía experimental.

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Animal experimentation provides important technical and scientific knowledge, mainly in the biomedical field, thus remaining the core of clinical studies and, consequently, causing a lot of controversy¹⁻³. Nowadays, studies using non-human animals also adhered to ethical parameters based on the concept of “well-being” of the research subject that are fundamental aspects to carry out the project^{3,4}.

Consequently, pain, suffering and hygiene when handling animals in a research project are aspects that should be observed, for methodological and ethical reasons, are shown, both by the scientific community and by international organizations of animal protection, to be important factors interfering with the final results of the research⁵⁻⁷. National and international legislations protect the rights and care of these animals, mainly regarding suffering and pain, being responsibility of the researchers to ensure the application of norms^{8,9}. Thus, it is not allowed to conduct a research in cases where the animal damage is greater than the gains of knowledge, and in cases where alternatives methods of research are applied^{1,5,8}.

Thus, with this situation that points to the continuous use of animals in clinical studies and to the need to eliminate or reduce the suffering to the animals used, this work has the purpose of raise the issue of using analgesia in experimental procedures with animals and the correct use of level of invasiveness.

Methods

A cross-sectional quantitative and observational study was conducted. Data were collected from July to November 2015. One hundred and six projects submitted to Animal Research Ethics Committee (AREC) of a Brazilian university were analyzed from December 2010 to December 2014. All projects that used animals in research participated in this research.

Projects were analyzed according to international ethical principles and norms for researches involving human beings (Resolution 466/2012 from the Conselho Nacional de Saúde¹⁰ (National Health Council)). As the object of study, research projects submitted to AREC were chosen – that protects the confidentiality of data of researchers –, that were evaluated and approved by the Ethics Committee of the state of Pará and then they were accepted by the director of AREC. Moreover, they are projects that

were authorized to use the database, protecting the confidentiality of the data on the investigation.

A research protocol was established and elaborated to collect data of medical charts from the hypothesis of research “Is there anything in the current legislation referring to analgesia of laboratory animals that undergo experimental surgeries in projects submitted to AREC?”, and of the literature consulted. Variables were statistically correlated by means of test G, with $p < 0.05$, comparing results with the current literature.

Results

Table 1. Projects submitted to AREC using the surgical technique in the methodology. 2010-2014, Belém/PA

Tested the surgical technique		
Yes*	68	64,2%
No	38	35,8%
Total	106	100%

* $p = 0.0049^*$ (Test G)

Table 2. Level of invasiveness, named by the researcher and correlated to the use of analgesia in projects submitted to AREC. 2010-2014, Belém/PA

Level of invasiveness	Analgesia			
	Yes		No	
GI1	2	12,5%	14	87,5%
GI2	8	32,0%	17	68,0%
GI3	10	23,8%	32	76,2%
GI4	3	42,9%	4	57,1%
Total	23	25,6%	67	74,4%

16 projects did not report

$p = 0,3837^*$ (Test G)

Table 3. Surgical procedures correlated to the use of analgesia in projects submitted to AREC. 2010-2014, Belém/PA

Surgery	Analgesia			
	Com		Sem	
Yes	22	34,4%	42	65,6%
No	1	3,8%	25	96,2%
Total	23	25,6%	67	74,4%

16 projects did not report

* $p = 0,0025^*$ (Test G)

Table 4. Level of invasiveness, named by the researcher, correlated to the surgical procedures of methods submitted to AREC. 2010-2014, Belém/PA

Level of invasiveness	Surgery			
	Yes		No	
G1	2	8,0%	23	92,0%
G2	16	55,2%	13	44,8%
G3	42	95,5%	2	4,5%
G4	8	100,0%	0	0,0%
Total	68	64,2%	38	35,8%

* $p < 0,0001$ * (Test G)

Discussion

No scientific gain may be justified based on the suffering of other living beings. Out of 106 projects submitted to Ceua of a public university, most (64.2%) employed surgery as the means or the end, according to what is defined in the methodological description of the study, with analgesia usually indicated in post-operative procedures, to ensure the well-being of patients. Therefore, analgesia is the ethical element that is important to be analyzed in details.

Pain is the essential element for survival and maintenance of life of complex organisms; however, its continuance reduces the quality of life, causes homeostatic instability and produces extremely harmful biochemical and behavioral reactions, as shown by Coutinho¹¹ and Andrade, Pinto e Oliveira¹². Despite the legislations and manuals dealing with this subject, and of data confirming the need to preserve the normal physiology, researchers still disregard animals' pain in experiments.

This carelessness may be verified mainly in experimental surgeries, since 65.6% of projects evaluated did not achieve analgesia, even with the use of surgical procedures, corroborating with data obtained in other AERC, as mentioned by Filipecki, Machado e Teixeira¹³ and Paixão⁹. There have been several justifications not to apply analgesia, with the most common justification used by researchers being the possible interference of painkillers in anatomopathological readings of liver and kidney structures, corresponding to 96% of justifications.

Nevertheless, even without a more careful analysis, this justification is shown to be inconsistent, since it would not be viable to apply the same technique, under the same conditions, in humans, since the surgical procedure is followed by an appropriate analgesia in the postoperative period. The stress caused by pain is shown to be more damaging

to pathological structures than any analgesic, due to the release of inflammatory mediators and of the behavioral changes, which may cause inappetence, acts of mutilation and sleep-wake changes, as mentioned by Kohn *et al.*,⁶ and other authors^{6,9}.

With the purpose of avoiding similar situations, Conselho Nacional de Controle de Experimentação Animal (Concea) (National Council of Animal Experimentation Control) produced stratification of the level of invasiveness (LI), in each procedure should be framed for better viewing of the level of pain presented by animals, which would consequently lead to a care with the analgesic protocol used. There are four levels of invasiveness: the first one refers to experiments that cause little or no discomfort or stress; the second one refers to a light intensity of discomfort or stress; the third one refers to an intermediate intensity of discomfort or stress; and the fourth one refers to experiments that cause high intensity of pain. However, what is observed in the studies analyzed is that even with the correct classification of the level of invasiveness, there was no proper attention given to analgesia, since only 34.4% of projects that performed the surgical procedure provided post-operative analgesia. With this evidence, it is worth repeating that no scientific gain is justified based on the suffering of other living beings.

It is the researcher's responsibility to do a follow-up of animals that underwent a surgery and to recognize signs of pain, not justifying the lack of analgesia in animals in experimental surgeries that have a certain level of invasiveness, as mentioned by several national organizations and international treaties. The level of invasiveness should not replace the clinical assessment and, for more comfort to the animal¹¹, light analgesia should be used in minimally invasive methodologies.

Final Considerations

Results obtained in the analysis of projects involving surgical procedures in non-human animals in Brazilian public universities, have shown total irregularity as for compliance with ethical standards, which regulate studies conducted with animals. Most of the 106 projects submitted to analysis of AREC used a surgical technique, and more half of them did not use postoperative analgesia, causing pain and suffering to animals that participated in the study. This alarming situation shows the urgent need to train and improve AREC assessors, who should be familiar with medications, dosages and

methodological parameters, to judge the discomfort of animals involved in the projects of the study. It is important that members of AREC are trained and, this enabled to verify the life conditions and handling situations of animals in visits to animal facilities, which should occur regularly to follow the procedures and the care adopted.

There should be a campaign in institutions of elucidation of ethical norm that regulate research with non-human animals in Brazil¹⁴, in order to train students and professor, in order to adopt the best research methodology available for their project, without promoting unnecessary and unjustified pain and suffering to animals participating in studies. It is also recommended regular forums do discuss, raise and debate issues regarding this topic,

such as the use of certain medications and their experimental-therapeutic doses, aiming at promoting conscience of the academic community on the best design and conduction of experiments.

In conclusion, the survey and the release of data statistically analyzed on experiments carried out in AREC helps the scientific community to know and to recognize complex and concomitantly delicate aspects of the use of non-human animals in researches, as well as to debate and improve the knowledge and practices adopted regarding this polemic issue, which is shown to be extremely important for scientific advance as mentioned by Zuanon, Benjamin and Fonseca¹⁵. Thus, further studies on the ethical parameters of animal researches are necessary.

Referências

1. Greek R, Greek J. Is the use of sentient animals in basic research justifiable?. *Philos Ethics Humanit Med.* 2010;5(14):23-9
2. Kalichman M. Evidence-Based Research Ethics. *Am J Bioeth.* 2009;9(6-7):85-7.
3. Miziara ID, Magalhães ATM, Santos MA, Gomes EF, Oliveira RA. Research ethics in animal models. *Braz J Otorhinolaryngol.* 2012;78(2):128-31.
4. Motta LCS, Vidal SV, Siqueira-Batista R. Bioética: afinal, o que é isto?. *Rev Bras Clin Med.* 2012;10(5):431-9.
5. Damy SB, Camargo RS, Chammas R, Figueiredo LFP. Aspectos fundamentais da experimentação animal: aplicações em cirurgia experimental. *Rev Assoc Med Bras.* 2010;56(1):103-11.
6. Kohn DF, Martin TE, Foley PL, Morris TH, Swindle MM, Vogler GA et al. Guidelines for the assessment and management of pain in rodents and rabbits. *J Am Assoc Lab Anim Sci.* 2007;46(2):97-108.
7. Schanaider A, Silva PC. Uso de animais em cirurgia experimental. *Acta Cir Bras.* 2004;19(4):441-7.
8. Brasil. Lei nº 11.794, de 8 de outubro de 2008. Regulamenta o inciso VII do § 1º do art. 225 da Constituição Federal, estabelecendo procedimentos para o uso científico de animais. In: *Coletânea legislativa ambiental.* São Paulo: Saraiva; 2011.
9. Paixão RL. Os desafios das comissões de ética no uso de animais. *Ciênc vet tróp.* 2008;11(1):84-7.
10. Brasil. Conselho Nacional de Saúde. Resolução nº 466, de 12 de dezembro de 2012. Diretrizes e normas regulamentadoras de pesquisas envolvendo seres humanos. Disponível: <http://bit.ly/1mTMIS3>
11. Coutinho AFOSV. Subjetividade na avaliação da dor animal [tese]. Lisboa: Universidade Técnica de Lisboa/Faculdade de Medicina Veterinária; 2012.
12. Andrade A, Pinto SC, Oliveira RS, organizadores. *Animais de laboratório: criação e experimentação.* Rio de Janeiro: Fiocruz; 2002.
13. Filipecki ATP, Machado CJS, Teixeira MO. Análise de uma experiência local de acompanhamento e controle de uso científico de animais na pesquisa biomédica. *Filos Hist Biol.* 2010;5(2):195-215.
14. Brasil. Ministério da Ciência, Tecnologia e Inovação. Conselho Nacional de Controle e Experimentação Animal. Normativas do Concea para produção, manutenção ou utilização de animais em atividades de ensino ou pesquisa científica. Brasília: Concea; 2015. Disponível: <http://bit.ly/2bOCmll>
15. Zuanon ACA, Benjamin LA, Fonseca CC. Contribuições para a adoção de uma cultura de divulgação, valorização e de respeito aos comitês e, ou, comissões de ética no uso de animais. *Rev. Ceres.* 2014;61(1):757-63.

Participation of the authors

Caio Botelho Brito is the author of the article. Rosa Helena and Nara Macedo Botelho acted as advisers and reviewers.

