Доклинические хирургические исследования: проблемы и перспективы

Ануров Михаил Владимирович
Ведущий научный сотрудник отдела экспериментальной хирургии НИИ клинической хирургии, д.м.н.
REVIEW

Limits to clinical trials in surgical areas

Marco Kawamura Demange, Felipe Fregni

1 Orthopaedics and Traumatology, Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Sao Paulo, Brasil. 2 Harvard Medical School.

Randomized clinical trials are considered to be the gold standard of evidence-based medicine nowadays. However, it is important that we point out some limitations of randomized clinical trials relating to surgical interventions.

BMJ VOLUME 324 15 JUNE 2002 bmj.com

Randomised trials in surgery: problems and possible solutions

Peter McCulloch, Irving Taylor, Mitsuru Sasako, Bryony Lovett, Damian Griffin

Some aspects of surgery present special difficulties for randomised trials

Ethical Issues of Participant Recruitment in Surgical Clinical Trials

Peter Angelos, MD, PhD, FACS

The nature of clinical trials in surgery raises ethical issues that are different from those outside of surgery.
Search Results
Showing 1,034 results for: experimental model

Modulating Portal Hemodynamics With Vascular Ring Allows Efficient Regeneration After Partial Hepatectomy in a Porcine Model
Bucur, Petru O.; Bekheit, Mohamed; Audebert, Chloe; More
To investigate safety and efficacy of temporary portal hemodynamics modulation with a novel percutaneously adjustable vascular ring (MID-AVR) onto a porcine model of 75% hepatectomy.

Stem Cell Mobilization Is Lifesaving in a Large Animal Preclinical Model of Acute Liver Failure
Ahmadi, Ali R.; Chicco, Maria; Wasson, Russell N.; More
Acute liver failure (ALF) affects 2000 Americans each year with no treatment options other than liver transplantation. We showed previously that mobilization of endogenous stem cells is protective against ALF in rodents. The objective of this study was to assess whether stem cell mobilizing drugs are lifesaving in a large...
Large and Small Animal Models

Orthopaedic
- Bone healing studies
- Internal fixation implant testing
- External fixation implant testing
- Allograft, autograft and xenograft testing
- Osteochondral defect/cartilage regeneration

Spine
- Lumbar interbody fusion
- Posterolateral intervertebral fusion - PLIF
- Cervical fusion
- Vertebroplasty
- Laminectomy

Soft Tissue
- Wound reconstruction/healing
- Urogenital implants
- Laparoscopic surgery

Osteoporosis
- Nutritional studies
- Hormonal studies
- Laparoscopic ovariectomy
GUIDE FOR THE CARE AND USE OF LABORATORY ANIMALS

Eighth Edition

Surgery, 115
Training, 115
Presurgical Planning, 116
Surgical Facilities, 116
Surgical Procedures, 117
Aseptic Technique, 118
Intraoperative Monitoring, 119
Postoperative Care, 119
Pain and Distress, 120
Anesthesia and Analgesia, 121
Euthanasia, 123
References, 124
B. Study Assurances

FDA recognizes that, for various reasons, use of a GLP facility may not be possible, such as when a highly specialized skill set of investigators is only available at a particular non-GLP facility. In these situations, FDA recommends that you provide a complete rationale for the selection of the test site, and that you follow the highest levels of oversight, record-keeping, and reporting. FDA also recommends that you hire an independent auditor so that impartial quality assurance is provided.
Доклинические хирургические исследования

1. Имплантация новых медицинских устройств для хирургии:
   - предрегистрационные исследования (реакция организма на имплантируемое устройство)
   - пострегистрационные исследования (функционирование имплантированного устройства)

2. Моделирование патологических процессов с целью разработки новых способов диагностики и хирургического лечения
   - исследование эффективности новых устройств в условиях модели патологического процесса

3. Создание моделей различных заболеваний для других медицинских специалистов и исследователей

4. Исследования, связанные с трансплантацией органов, замещением их функций и протезированием тканей
The role of a surgical facility manager (SFM) within a laboratory animal surgical facility, or surgery department, has changed significantly over the past 15–20 years. Historically, because of their advanced training and experience, veterinarians were usually involved in managing surgical facilities in a research environment. However, in recent years, because of increased veterinary animal care and use responsibilities, in some instances this has resulted in nonveterinarians assuming that role. In either case, a
Персонал

У сотрудников должно быть понимание выполняемых хирургических процедур и их клинического значения, знание современного хирургического оборудования и анестезиологической аппаратуры.

Сотрудники должны уметь творчески моделировать, а не копировать клиническую ситуацию.
Организация и планирование.

1. Участие сотрудников хирургического подразделения в планировании экспериментального исследования еще на этапе формирования заявки в IACUC

2. Выполнение пилотного проекта, которое облегчает создание протокола, подаваемого в IACUC, и проведение эксперимента с соблюдением принципа 3 R
Организация помещений

Помещение для подготовки хирургов

Комната подготовки животных

Стерилизационная

Комната восстановления
Операции у грызунов с соблюдением правил асептики

Обкладка операционного поля стерильной пленкой или салфеткой

Использование стерильных хирургических инструментов и перчаток
Оснащение операционных

Экспериментальная операционная

Экспериментальная рентгеноперационная

Лапароскопическая стойка
Имплантируемые медицинские устройства

Водитель ритма

Сетчатый протез для герниопластики

Сердечный клапан

Внутрисосудистый стент
Conventional and Specific-Pathogen Free Rats Respond Differently to Anesthesia and Surgical Trauma

Hayley L. Letson, Jodie Morris, Erik Biros & Geoffrey P. Dobson

using rotational thromboelastometry. Health screening was outsourced to Cerberus Sciences. SPF rats had significantly lower pulse pressure (38% decrease), arrhythmias and prolonged QTc (27% increase) compared to conventional rats. No arrhythmias were found in conventional rats. SPF rats had significantly higher white cell, monocyte, neutrophil and lymphocyte counts, and were hyperfibrinolytic, indicated by EXTEM maximum lysis >15%. Independent assessment revealed similar pathogen exclusion between colonies, with the exception of *Proteus* in SPF animals. Returning to a conventional facility restored normal host physiology. We conclude that SPF animals displayed an abnormal hemodynamic, hematological and hemostatic phenotype in response to anesthesia and surgery, and provide a number of recommendations to help standardize research outcomes and translation.
# Surgical and Anesthetic Record

(Large Animal)

<table>
<thead>
<tr>
<th>Protocol Information</th>
<th>Personnel Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol #:</td>
<td>LR:</td>
</tr>
<tr>
<td>Species</td>
<td>Surgeon:</td>
</tr>
<tr>
<td>Animal ID #:</td>
<td>Assistant Surgeon:</td>
</tr>
<tr>
<td>Animal Name:</td>
<td>Anesthetist:</td>
</tr>
<tr>
<td>Procedure Date:</td>
<td>Assistant:</td>
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</tbody>
</table>

## Surgical Procedures:

## Preoperative Exam, Preparation, & Physical Condition of Animal:
(i.e., describe any abnormalities and signs of injury, illness, lack of appetite, diarrhea, etc.)

## Baseline Values

<table>
<thead>
<tr>
<th>Wt (kg):</th>
<th>IV catheter:</th>
<th>Surgery Start Time:</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR:</td>
<td>Endotracheal tube size:</td>
<td>Surgery End Time:</td>
</tr>
<tr>
<td>RR:</td>
<td>Ointment placed in eyes:</td>
<td>Time Returned to Cage:</td>
</tr>
<tr>
<td>Temp:</td>
<td>Supplemental heat supplied:</td>
<td></td>
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</tbody>
</table>

## PERIOPERATIVE TREATMENTS

<table>
<thead>
<tr>
<th>Time</th>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>Dose (ml or other)</th>
<th>Route</th>
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## MONITORING PARAMETERS & TREATMENTS DURING SURGERY

The following parameters, at a minimum (or as described in the approved IACUC protocol) must be recorded every 15 minutes starting from administration of the pre-anesthetic, throughout surgery, and continued until animal is recovered from the anesthesia.

<table>
<thead>
<tr>
<th>Time</th>
<th>% Anesthetic Gas</th>
<th>End Tidal CO₂</th>
<th>HR</th>
<th>RR</th>
<th>O₂ Sat</th>
<th>Mucous Membranes (e.g., pink, pale, cyanotic)</th>
<th>Anesthetic Level</th>
<th>Fluids (running total of volume administered)</th>
<th>Temp</th>
<th>Comments</th>
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</table>
# Surgical and Anesthetic Record

**Rodent**

<table>
<thead>
<tr>
<th>Protocol Information</th>
<th>Personnel Information</th>
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<tbody>
<tr>
<td>Protocol #:</td>
<td>Lead Researcher:</td>
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<tr>
<td>Species:</td>
<td>Surgeon:</td>
</tr>
<tr>
<td>Procedure Date:</td>
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</table>

**Surgical Procedure(s):**

**MONITORING PARAMETERS & TREATMENTS DURING SURGERY**

The following parameters, at a minimum (or as described in the approved IACUC protocol) must be recorded. (Note: if isoflurane is only drug that is used, animal weight does not need to be recorded. Please make note of any re-dosing of drug.)

<table>
<thead>
<tr>
<th>Animal ID</th>
<th>Weight</th>
<th>Anesthetic Name</th>
<th>Dosage (mg/kg)</th>
<th>Dosage (mg/animal)</th>
<th>Analgesic Name</th>
<th>Dosage (mg/kg)</th>
<th>Comments</th>
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The ARRIVE Guidelines Checklist
Animal Research: Reporting In Vivo Experiments
Carol Kilkenny, William J Browne, Innes C Cuthill, Michael Emerson and Douglas G Altman

<table>
<thead>
<tr>
<th>ITEM</th>
<th>RECOMMENDATION</th>
<th>Section/Paragraph</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td>1. Provide as accurate and concise a description of the content of the article as possible.</td>
<td></td>
</tr>
<tr>
<td>Abstract</td>
<td>2. Provide an accurate summary of the background, research objectives, including details of the species or strain of animal used, key methods, principal findings and conclusions of the study.</td>
<td></td>
</tr>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
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</tr>
</tbody>
</table>
| Background            | 3. a. Include sufficient scientific background (including relevant references to previous work) to understand the motivation and context for the study, and explain the experimental approach and rationale.  
                      | b. Explain how and why the animal species and model being used can address the scientific objectives and, where appropriate, the study’s relevance to human biology. |                   |
| Objectives            | 4. Clearly describe the primary and any secondary objectives of the study, or specific hypotheses being tested. |                   |
| **METHODS**           |                                                                               |                   |
| Ethical statement     | 5. Indicate the nature of the ethical review permissions, relevant licences (e.g. Animal [Scientific Procedures] Act 1985), and national or institutional guidelines for the care and use of animals, that cover the research. |                   |
| Study design          | 6. For each experiment, give brief details of the study design including: 
                      | a. The number of experimental and control groups.  
                      | b. Any steps taken to minimise the effects of subjective bias when allocating animals to treatment (e.g. randomisation procedure) and when assessing results (e.g. if done, describe who was blinded and when).  
                      | c. The experimental unit (e.g. a single animal, group or cage of animals). 
                      | A time-line diagram or flow chart can be useful to illustrate how complex study designs were carried out. |                   |
| Experimental procedures| 7. For each experiment and each experimental group, including controls, provide precise details of all procedures carried out. For example: 
                      | a. How (e.g. drug formulation and dose, site and route of administration, anaesthesia and analgesia used [including monitoring], surgical procedure, method of euthanasia). Provide details of any specialist equipment used, including supplier(s).  
                      | b. When (e.g. time of day).  
                      | c. Where (e.g. home cage, laboratory, water maze).  
                      | d. Why (e.g. rationale for choice of specific anaesthetic, route of administration, drug dose used). |                   |
| Experimental animals  | 8. a. Provide details of the animals used, including species, strain, sex, developmental stage (e.g. mean or median age plus age range) and weight (e.g. mean or median weight plus weight range).  
                      | b. Provide further relevant information such as the source of animals, international strain nomenclature, genetic modification status (e.g. knock-out or transgenic), genotype, health/immune status, drug or test naïve, previous procedures, etc. |                   |
| **RESULTS**           |                                                                               |                   |
| Housing and husbandry | 9. a. Provide details of: 
                      | b. Husbandry conditions (e.g. breeding programme, light/dark cycle, temperature, quality of water etc for fish, type of food, access to food and water, enrichment).  
                      | c. Welfare-related assessments and interventions that were carried out prior to, during, or after the experiment. |                   |
| Sample size           | 10. a. Specify the total number of animals used in each experiment, and the number of animals in each experimental group.  
                      | b. Explain how the number of animals was arrived at. Provide details of any sample size calculation used.  
                      | c. Indicate the number of independent replications of each experiment, if relevant. |                   |
| Allocating animals to  | 11. a. Give full details of how animals were allocated to experimental groups, including randomisation or matching if done.  
                      | experimental groups |                   |
| Experimental outcomes | 12. Clearly define the primary and secondary experimental outcomes assessed (e.g. cell death, molecular markers, behavioural changes). |                   |
| Statistical methods   | 13. a. Provide details of the statistical methods used for each analysis.  
                      | b. Specify the unit of analysis for each dataset (e.g. single animal, group of animals, single neuron).  
                      | c. Describe any methods used to assess whether the data met the assumptions of the statistical approach. |                   |
| **DISCUSSION**        |                                                                               |                   |
| Interpretation/        | 18. a. Interpret the results, taking into account the study objectives and hypotheses, current theory and other relevant studies in the literature.  
                      | scientific implications | b. Comment on the study limitations including any potential sources of bias, any limitations of the animal model, and the imprecision associated with the results.  
                      | c. Describe any implications of your experimental methods or findings for the replacement, refinement or reduction (the 3Rs) of the use of animals in research. |                   |
| Generalisability/      | 19. Comment on whether, and how, the findings of this study are likely to translate to other species of systems, including any relevance to human biology. |                   |
| translation            |                                                                               |                   |
| Funding                | 20. List all funding sources (including grant number) and the role of the funder(s) in the study. |                   |
Резюме

На сегодняшний день, несмотря на высокую потребность, в большинстве конвенциональных виварий возможно проведение очень ограниченного числа хирургических исследований. К ним можно отнести, и то условно, только острые эксперименты с использованием грызунов.
Сопутствующие проблемы

Отсутствие экспериментальных лабораторий для проведения хирургических исследований надлежащего уровня порождает проблемы, выходящие за рамки собственно исследований. Создаются альтернативные площадки не контролируемых исследований и тренингов.
Перспективы

Согласно последнему анализу Evaluate Ltd, мировая отрасль медицинских устройств будет расти в совокупном годовом темпе на 5,6%, достигнет 595 миллиардов долларов к 2024 г.

Общие расходы на исследования и разработки в области медтехники будут расти ежегодно на 4,5% и к 2024 году составят 39 млрд. долларов.

Быстрорастущие области производства медицинских изделий - кардиология, диагностическая визуализация, ортопедия, офтальмология, общая и пластическая хирургия, эндоскопия, доставка лекарств, неврология и нейрохирургия, лечение диабета.
Результаты сотрудничества

• 80 совместных экспериментальных проектов
• 17 диссертаций
• 67 публикаций
• 38 исследовательских грантов (DFG, INTAS, медицинские и фармакологические компании)
Исследование имплантируемых биоматериалов

Центральный разрыв протеза

Оксидативное повреждение волокна

Central rupture and bulging of low-weight polypropylene mesh following recurrent incisional sublay hernioplasty

M. Žuvela · D. Galun · A. Djurić-Stefanović ·
I. Palibek · M. Petrović · M. Miličević
Изучение ранних биомаркеров ишемического повреждения кишки при странгуляционной непроходимости