International Journal of Molecular Veterinary Research 2024, Vol.14, No.3, 98-107
http://animalscipublisher.com/index.php/ijmvr

Research Insight Open Access

Evaluating the Impact of Analgesics on Animal Welfare in Oncology Research

Jinya Li, Mengyue Chen
Animal Science Research Center, Cuixi Academy of Biotechnology, Zhuji, 311800, Zhejiang, China
Corresponding author: mengyue.chen@cuixi.org

International Journal of Molecular Veterinary Research, 2024, Vol.14, No.3 doi: 10.5376/ijmvr.2024.14.0012
Received: 27 Feb., 2024
Accepted: 18 Apr., 2024
Published: 16 May., 2024

Preferred citation for this article:
Li J.Y., and Chen M.Y., 2024, Evaluating the impact of analgesics on animal welfare in oncology research, International Journal of Molecular Veterinary Research, 14(3): 98-107 (doi: 10.5376/ijmvr.2024.14.0012)

Abstract The use of analgesics in oncology research involving animal models is critical to ensuring both ethical standards and scientific validity. This study evaluates the impact of analgesics on animal welfare and research outcomes in oncology, focusing on the balance between effective pain management and the integrity of experimental data. Through the examination of various analgesics, including opioids and non-steroidal anti-inflammatory drugs (NSAIDs), the study highlights their differing effects on pain relief, tumor growth, and overall animal well-being. Key findings reveal that while certain analgesics can improve animal welfare by reducing pain and stress, they may also introduce variability in research outcomes due to their influence on physiological processes critical to cancer research. The study underscores the need for a comprehensive approach to pain management that prioritizes both animal welfare and the reliability of research data. Recommendations for future research include the development of novel analgesics, improved pain assessment tools, and adherence to ethical frameworks that ensure consistent application of pain management protocols in oncology research.

Keywords Analgesics; Animal welfare; Oncology research; Pain management; Tumor growth; Ethical considerations

1 Introduction

Oncology research in animals is a critical component of understanding cancer mechanisms and developing effective treatments. Animal models, particularly rodents, are extensively used to study cancer biology, including tumor development, metastasis, and response to therapies (Workman et al., 2010; Taylor, 2019). Comparative oncology, which involves studying cancer in companion animals like dogs, has also gained traction due to its translational potential for human cancer therapies (Garden et al., 2018; LeBlanc and Mazcko, 2020). These models provide invaluable insights that are often not possible through in vitro studies alone.

Animal welfare is a fundamental aspect of ethical research practices. Ensuring the well-being of animals used in research is not only a moral obligation but also a scientific necessity, as stress and pain can significantly affect experimental outcomes (Workman et al., 2010; Pound and Nicol, 2018). Guidelines such as the 3Rs (Replacement, Reduction, and Refinement) are established to minimize animal suffering and improve the quality of research data (Workman et al., 2010). However, studies have shown that the implementation of these guidelines is inconsistent, with many animals experiencing significant pain and distress during experiments (Pound and Nicol, 2018; Herrmann and Flecknell, 2019).

Analgesics play a crucial role in managing pain in animal models used in oncology research. Pain management is essential to prevent stress-induced alterations in immune function and other physiological processes that can confound research results (Clutton, 2018; Taylor, 2019). Opioids and non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used analgesics, each with distinct effects on cancer progression and metastasis. For instance, NSAIDs have been shown to reduce the risk of metastasis, whereas opioids may have the opposite effect (Hooijmans et al., 2015; Taylor, 2019). The choice and administration of analgesics must be carefully considered to balance animal welfare with the integrity of the research data (Slingsby, 2010; Clutton, 2018).

This study evaluates the impact of analgesic use on animal welfare and the effectiveness of oncology research outcomes. The research will explore how different analgesics affect pain management, stress levels, and cancer progression, providing evidence-based recommendations for the use of analgesics in oncology studies. The aim is

to prioritize animal welfare without compromising the scientific validity of the research. By examining the intersection of analgesic use, animal welfare, and the integrity of oncology research, this study offers a comprehensive assessment that could inform future guidelines and practices in this field. The study aspires to contribute to the improvement of current practices and enhance ethical standards in animal oncology research.

2 Common Analgesics Used in Oncology Research

2.1 Types of analgesics

In oncology research, the primary classes of analgesics used to manage pain in animal models include opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and local anesthetics. Opioids, such as morphine and fentanyl, are potent analgesics that act on the central nervous system to alleviate severe pain. NSAIDs, including drugs like ibuprofen and ketoprofen, are commonly used for their anti-inflammatory and analgesic properties, particularly in cases of inflammatory pain (Pchelintsev, 2020; Liu et al., 2021). Local anesthetics, such as lidocaine and bupivacaine, are used to block nerve conduction in specific areas, providing targeted pain relief (Hooijmans et al., 2015; Herskin and Nielsen, 2018; Stillman and Whittaker, 2019).

2.2 Mechanisms of action

The mechanisms of action for these analgesics vary significantly. Opioids function by binding to opioid receptors in the brain and spinal cord, inhibiting the transmission of pain signals and altering the perception of pain (Stillman and Whittaker, 2019). NSAIDs work by inhibiting cyclooxygenase (COX) enzymes, which play a crucial role in the synthesis of prostaglandins that mediate inflammation and pain (Hooijmans et al., 2015; Winder et al., 2018). Local anesthetics block sodium channels on nerve cells, preventing the initiation and propagation of nerve impulses, thereby providing localized pain relief (Grandhi and Perona, 2019).

2.3 Dosage and administration in various animal models

The dosage and administration of analgesics in animal models depend on the species, the type of pain, and the specific analgesic used. For instance, in sheep, opioids are often administered at higher doses due to their short-acting nature and variable efficacy (Stillman and Whittaker, 2019). NSAIDs are typically used in cases of inflammatory pain and are administered based on the severity and duration of the pain (Herskin and Nielsen, 2018; Winder et al., 2018). Local anesthetics are applied directly to the site of pain or administered via regional blocks to provide targeted analgesia (Grandhi and Perona, 2019). The administration protocols must be carefully tailored to each animal model to ensure effective pain management while minimizing adverse effects (Herrmann and Flecknell, 2019; Huss et al., 2019).

2.4 Comparison of efficacy and safety profiles

The efficacy and safety profiles of these analgesics vary. Opioids are highly effective for severe pain but can cause significant side effects, including respiratory depression and tolerance with long-term use (Huss et al., 2019; Stillman and Whittaker, 2019). NSAIDs are effective for inflammatory pain and have a favorable safety profile when used short-term, but long-term use can lead to gastrointestinal and renal complications (Hooijmans et al., 2015; Winder et al., 2018).

Local anesthetics are generally safe and effective for localized pain relief, but their use is limited by the duration of action and potential for systemic toxicity if not administered correctly (Grandhi and Perona, 2019). Combining NSAIDs with local anesthetics has been shown to enhance pain relief and reduce the need for opioids, thereby minimizing the risk of opioid-related side effects (Herskin and Nielsen, 2018).

3 Impact of Analgesics on Animal Welfare

3.1 Assessment of pain relief

The assessment of pain relief in animal models is crucial for ensuring both ethical standards and the validity of research outcomes. Pain has a profound effect on an animal's well-being, and unalleviated pain can introduce significant variability in experimental data (Herrmann and Flecknell, 2019). Effective pain management is essential, as untreated pain can act as a stressor, leading to immune system perturbations and other physiological changes that may confound research results (Taylor, 2019).

Lofgren et al. (2018) investigated the effects of analgesics, particularly meloxicam and buprenorphine, on tumor growth in mouse cancer models. The results showed that while surgery associated with tumor inoculation increased tumor growth and metastasis, especially in the mammary carcinoma model, the use of buprenorphine, especially in repeated doses, mitigated these effects. In the melanoma model, meloxicam was shown to reduce lung metastasis. The use of analgesics can improve animal welfare without significantly impacting the scientific outcomes of cancer research. Proper pain management can reduce the confounding effects of surgical stress, potentially leading to more accurate and translatable cancer models (Figure 1).

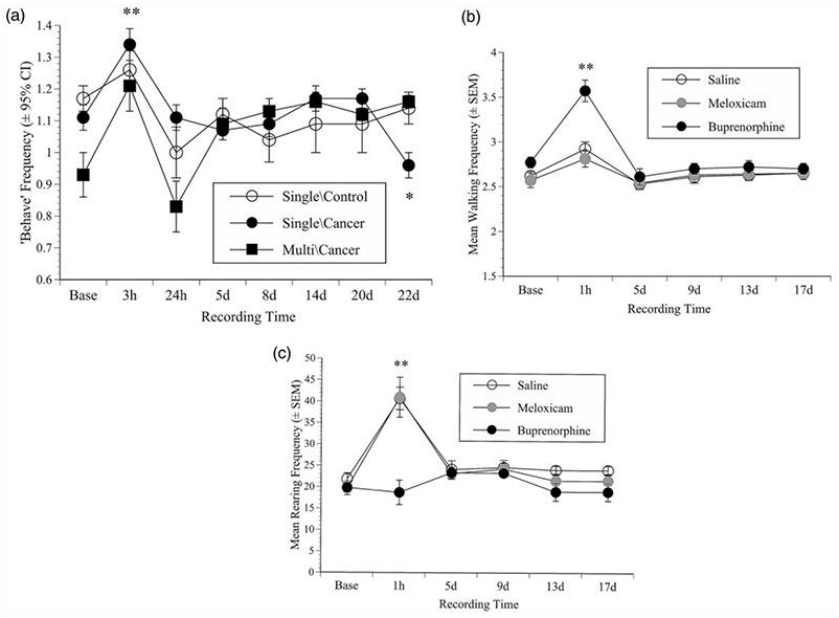

Figure 1 Behaviour results (Adopted from Lofgren et al., 2018)

Image caption: The figure shows the behavioral changes in mice in the 4T1 mammary carcinoma and B16 melanoma models. Figure a indicates that as the 4T1 tumor grows, spontaneous activity in the mice gradually decreases, particularly in the late stages of tumor development, suggesting an inhibitory effect of the tumor on mouse behavior. Figures b and c illustrate the walking and rearing behaviors in the B16 model, where mice treated with buprenorphine exhibited significant behavioral changes within 1 hour after tumor inoculation, with increased walking and decreased rearing. These results reveal the differential impact of tumors and analgesics on mouse behavior, highlighting the importance of pain management in the behavioral responses of experimental animals (Adapted from Lofgren et al., 2018)

3.2 Behavioral and physiological indicators of well-being

In animal experiments, behavioral and physiological indicators are crucial tools for assessing animal welfare. These indicators can reflect the levels of pain and overall health status of the animals. Pain not only leads to abnormal behaviors, such as reduced activity, abnormal postures, or self-mutilation, but also triggers physiological stress responses, including increased heart rate, elevated blood pressure, and changes in hormone levels (Peterson et al., 2017). These changes not only affect the welfare of the animals but may also interfere with the accuracy of experimental data. Therefore, researchers must closely monitor these indicators to minimize the impact of the experimental environment on the animals.

The use of appropriate analgesics can effectively reduce pain-induced behavioral and physiological abnormalities, thereby improving animal welfare. However, the selection of analgesics must be made with caution, as different drugs may have varying effects on physiological parameters and behavioral responses, potentially introducing additional variability (Clutton, 2018). Furthermore, the dosage, administration route, and timing of analgesics must be adjusted according to the specific requirements of the experiment to ensure that pain relief does not compromise the reliability of the experimental results. Thus, when designing and conducting animal experiments, researchers must comprehensively consider various factors to optimize analgesic strategies while ensuring the scientific validity of the data.

3.3 Side effects and long-term implications

The side effects and long-term implications of analgesic use in animal research are complex and multifaceted. Opioids and non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used analgesics, each with distinct effects on physiological processes such as immune function, cell proliferation, and apoptosis (Hooijmans et al., 2015; Taylor, 2019). While NSAIDs have been shown to reduce the risk of metastasis in cancer models, opioids may have immunomodulatory effects that could potentially influence research outcomes (Guimarães-Pereira, 2016). Additionally, the long-term use of analgesics can lead to tolerance and other side effects that may impact the overall health and well-being of the animals (Taylor, 2019).

3.4 Influence on research outcomes

The influence of analgesics on research outcomes is a critical consideration in experimental design. Both pain and the analgesics used to manage it can act as confounding factors, potentially affecting the validity and reproducibility of research findings. For example, analgesics can modulate immune responses and other physiological processes that are often the focus of biomedical research (Carbone and Austin, 2016; Taylor, 2019). Therefore, it is essential to balance the ethical obligation to alleviate pain with the need to maintain the integrity of the research data. Transparent reporting of analgesic use and its potential effects on study outcomes is necessary to ensure the reliability and reproducibility of scientific research (Carbone and Austin, 2016; Peterson et al., 2017).

4 Ethical Considerations

4.1 Ethical frameworks in animal research

Ethical frameworks in animal research are designed to ensure that the welfare of animals is prioritized while balancing the scientific objectives of the research. The Institutional Animal Care and Use Committee (IACUC) plays a crucial role in this process by evaluating the ethical implications of proposed experiments. They must consider the limits of available information on animal suffering, the effectiveness of analgesics, and the potential benefits of the research (Carbone, 2019). The harm-benefit analysis (HBA) is a cornerstone of this ethical evaluation, weighing the anticipated benefits of the research against the predicted harms to the animals (Pound and Nicol, 2018). This process is essential for maintaining ethical standards and ensuring that animal welfare is not compromised for scientific gain.

4.2 Regulatory guidelines for analgesic use

Regulatory guidelines mandate the use of analgesics to minimize pain and distress in laboratory animals. In Germany, for example, researchers are legally required to reduce any possible pain, suffering, distress, or lasting harm to an absolute minimum (Herrmann and Flecknell, 2019). However, compliance with these regulations is not always consistent. A retrospective review of animal research proposals revealed that postoperative analgesia was not proposed for 30% of surgeries, highlighting a gap between regulatory requirements and actual practice. Furthermore, the ARRIVE guidelines, which aim to improve the reporting of animal research, do not always influence the completeness of information on analgesic use in published studies (Carbone and Austin, 2016). This indicates a need for stricter adherence to and enforcement of regulatory guidelines to ensure animal welfare.

4.3 Balancing pain management and research integrity

Balancing pain management with research integrity is a significant challenge in oncology research. Both pain and the analgesics used to manage it can affect research outcomes, particularly in studies involving cancer models. Untreated pain can act as a stressor, leading to immune system perturbations, while analgesics can have immunomodulatory effects that may confound study results (Taylor, 2019). Therefore, researchers must carefully consider the choice of analgesics and their potential impact on the validity of the data. This requires a thorough understanding of analgesic pharmacology and its implications for the specific research objectives (Clutton, 2018). Effective pain management strategies should be integrated into the study design to ensure both animal welfare and the integrity of the research data.

Ethical considerations in animal research, particularly in oncology, require a delicate balance between minimizing animal suffering and maintaining the scientific validity of the research. Regulatory guidelines provide a framework for this balance, but consistent adherence and enforcement are necessary to ensure that animal welfare

is not compromised. Researchers must also be mindful of the potential impacts of pain and analgesics on their study outcomes, integrating effective pain management strategies into their experimental designs.

5 Case Study

5.1 Analysis of the effects of butorphanol on tumor growth and postoperative survival rate in a mouse model of ovarian cancer

In preclinical cancer research, animal models are widely used to evaluate the efficacy of anticancer drugs. However, the application of postoperative pain management in these models remains controversial, as some studies suggest that analgesics might influence tumor growth and treatment outcomes.

Butorphanol is a potent opioid analgesic commonly used for postoperative pain relief. A study investigated the effects of intraoperative use of butorphanol on tumor growth in a preclinical ovarian cancer model (Bratcher et al., 2019). The study involved 150 CB17 SCID mice, divided into a control group and a butorphanol-treated group. Butorphanol was administered as an analgesic during and after surgery. The study found no significant impact on the tumor implantation rate and growth speed in the butorphanol-treated group (Figure 2). Although there was a higher mortality rate observed in the butorphanol-treated mice within 24 to 48 hours post-surgery, the difference was not statistically significant. The results suggest that butorphanol does not negatively affect tumor growth in the short term, and the potential pain and stress caused by the absence of analgesics in experimental models might be of greater concern. The study emphasizes the importance of applying appropriate analgesics in preclinical tumor models and recommends further investigation into the effects of butorphanol across different tumor cell lines and mouse strains, which could contribute to improving animal welfare in experiments.

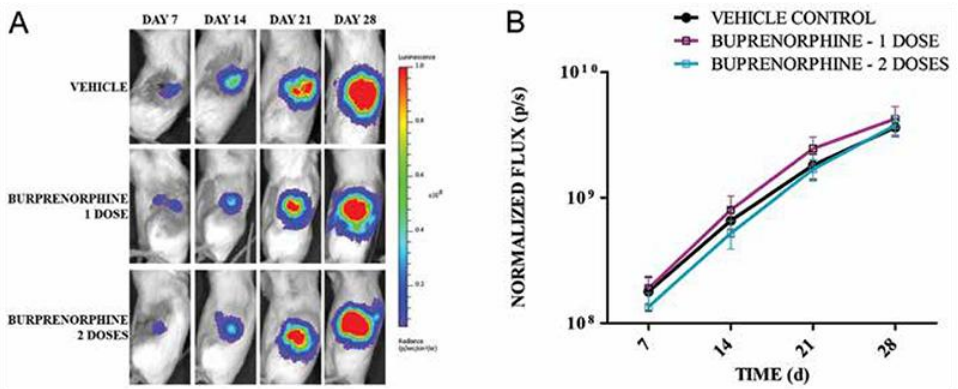

Figure 2 Buprenorphine does not significantly affect engraftment or growth of OVCAR-5 OT LMC cells implanted in ovary (Adopted from Bratcher et al., 2019)

Image caption: A) Representative longitudinal bioluminescent images of an individual mouse across all 3 treatment groups. All image thresholds are set to the same scale to facilitate comparison. B) Bioluminescent images of each group (n = 50 mice per group) were acquired weekly after surgical implantation of OVCAR-5 OT LMC cells. The average normalized flux (photons/s) ± 95% confidence interval is shown for each group. The images indicate no significant difference in tumor fluorescence intensity between the buprenorphine-treated groups and the control group, suggesting that short-term use of buprenorphine during and after surgery does not affect tumor growth rate. The results support the study's conclusion that buprenorphine does not interfere with tumor engraftment and growth in an ovarian cancer mouse model, validating the feasibility of using appropriate analgesics in such preclinical models (Adapted from Bratcher et al., 2019)

5.2 Evaluation of the effects of carprofen and buprenorphine in a mouse model of prostate cancer bone metastasis

Prostate cancer bone metastasis is a critical issue in oncology research, and mouse models are commonly used to study its progression and potential treatments. However, the invasive procedures involved in these studies, such as tumor cell injection, can cause significant pain. Due to concerns that analgesics might affect tumor growth, researchers often choose not to use pain relief in these experiments.

Xu et al. (2021) selected two commonly used analgesics, Carprofen and Buprenorphine, to evaluate their application in a mouse model of prostate cancer bone metastasis, investigating whether these analgesics would

significantly affect tumor growth. The mice received intratibial injections of prostate cancer cells and were randomly assigned to the analgesic groups (Carprofen or Buprenorphine) or a control group (saline) at the time of injection. The experiment lasted for four weeks, during which tumor growth and welfare indicators were monitored through bioluminescent imaging, X-rays, and behavioral assessments (including pain perception, activity levels, and weight changes). The results showed that neither Carprofen nor Buprenorphine had a significant impact on tumor growth. Tumor burden, measured by bioluminescent imaging, did not differ significantly among the treatment groups (Xu et al., 2021). Additionally, there was no significant improvement in pain perception, activity levels, or weight changes in the mice due to the use of analgesics.

The findings indicate that the single use of Carprofen or Buprenorphine does not significantly affect tumor growth in a mouse model of prostate cancer bone metastasis, with limited improvement in the welfare of the mice. The study provides valuable insights into the use of analgesics in oncology research, suggesting that in some prostate cancer bone metastasis models, the use of pain relief is feasible and unlikely to interfere with tumor growth. While the current findings show limited pain relief for mice, continued use of analgesics is supported, as it holds potential for improving animal welfare in experiments.

5.3 Pain management and challenges in sheep in biomedical research

Sheep, due to their physiological characteristics and size, are suitable animal models for biomedical research, especially in surgical studies. Stillman and Whittaker (2019) analyzed the effectiveness of various analgesics, including opioids, α 2-adrenoceptor agonists, nonsteroidal anti-inflammatory drugs (NSAIDs), and local anesthetics.

The study found that the analgesic effects of opioids in sheep are controversial, although the introduction of new opioid drugs has helped improve their effectiveness. NSAIDs have limited pain relief effectiveness in the absence of inflammation, while α 2-adrenoceptor agonists provide effective pain relief but are associated with side effects such as pulmonary edema and hypoxemia, which limit their use (Stillman and Whittaker, 2019). Local anesthetics are gradually being phased out due to their side effects, although they still hold value in combined anesthesia. The study recommends further exploration of NMDA receptor antagonists, such as ketamine, for pain management in sheep to fill the current gaps in research and enhance the welfare of experimental animals.

6 Challenges and Limitations

6.1 Variability in analgesic responses across species

One of the primary challenges in evaluating the impact of analgesics on animal welfare in oncology research is the variability in analgesic responses across different species. This variability can significantly affect the outcomes of studies and the generalizability of the results. For instance, the pharmacokinetics and pharmacodynamics of analgesics can differ widely between species, making it difficult to standardize pain management protocols (Clutton, 2018; Paterson and Turner, 2022).

Research has shown that while some analgesics may be effective in one species, they may not provide the same level of pain relief in another, or could even cause adverse effects (Hooijmans et al., 2019; Paterson and Turner, 2022). This inconsistency necessitates species-specific studies to determine the most effective and safe analgesic protocols, which can be resource-intensive and time-consuming.

6.2 Technical challenges in pain assessment

Accurately assessing pain in animals is another significant challenge. Unlike humans, animals cannot verbally communicate their pain, making it necessary to rely on behavioral and physiological indicators, which can be subjective and difficult to quantify (Tomacheuski et al., 2020; Paterson and Turner, 2022). The lack of validated pain assessment tools for many species further complicates this issue. For example, in research primates, there is a notable absence of objective pain assessment methods, leading to inconsistencies in pain management practices (Paterson and Turner, 2022). Additionally, the development of more effective biomarkers for pain, such as those identified through advanced proteomics techniques, is still in its early stages and requires further validation (Ghodasara et al., 2021).

6.3 Limitations in current research methodologies

Current research methodologies also present limitations in the study of analgesics and their impact on animal welfare. Many studies suffer from poor design and reporting, leading to a high risk of bias and unreliable results (Hooijmans et al., 2019). For instance, a meta-analysis of studies on chemotherapy-induced peripheral neuropathy highlighted the poor reporting and unclear risk of bias in many experiments, which undermines the reliability of the findings.

Furthermore, retrospective reviews of animal research proposals have revealed that postoperative analgesia is often inadequately addressed, with some studies not proposing any pain relief measures at all (Herrmann and Flecknell, 2019). This lack of rigorous methodology not only affects the welfare of the animals but also the validity of the scientific data generated. There is a pressing need for improved research designs, adherence to guidelines, and better training for researchers to ensure both ethical and scientific standards are met (Pound and Nicol, 2018; Herrmann and Flecknell, 2019). By addressing these challenges and limitations, the field can move towards more reliable and humane practices in oncology research involving animals.

7 Future Directions

7.1 Innovations in analgesic development

The development of new analgesics tailored for use in animal models is crucial for improving animal welfare in oncology research. Current analgesics, such as opioids and NSAIDs, have been shown to influence immune system function and cancer progression, which can confound experimental results (Demarco and Nunamaker, 2019; Taylor, 2019). Future research should focus on creating analgesics that minimize these side effects while effectively managing pain. Additionally, there is a need for more comprehensive studies on the pharmacokinetics and pharmacodynamics of these drugs in different animal species to ensure their efficacy and safety (Clutton, 2018; Hooijmans et al., 2019).

7.2 Advances in pain assessment tools

Accurate pain assessment is essential for the effective management of pain in animal models. Current methods often lack the sensitivity and specificity needed to detect varying levels of pain, leading to either over- or under-treatment (Herrmann and Flecknell, 2019; Tomacheuski et al., 2020). Future research should aim to develop more sophisticated pain assessment tools that can provide real-time, objective measurements of pain. These tools could include advancements in imaging technologies, biomarkers, and behavioral analysis software. Improved pain assessment will not only enhance animal welfare but also improve the reliability of experimental data by ensuring consistent pain management (Hutson et al., 2019; Martin et al., 2019).

7.3 Integration of welfare considerations in study design

Incorporating welfare considerations into the design of oncology studies is essential for ethical and scientific reasons. Studies have shown that unalleviated pain can significantly affect physiological parameters, thereby impacting the validity of research findings (Pound and Nicol, 2018; Taylor, 2019). Future research should focus on developing guidelines and frameworks that integrate welfare considerations from the planning stages of experiments. This includes the use of harm-benefit analyses to weigh the potential scientific gains against the welfare costs to the animals involved (Pound and Nicol, 2018). Additionally, adherence to guidelines such as PREPARE and ARRIVE should be enforced to ensure that welfare considerations are consistently applied (Herrmann and Flecknell, 2019).

7.4 Recommendations for future research

To advance the field of analgesic use in oncology research, several key areas need to be addressed. There is a need for more systematic reviews and meta-analyses to evaluate the efficacy and safety of different analgesics across various animal models (Hooijmans et al., 2019). Educational programs should be developed to train researchers in pain assessment and management techniques, as gaps in knowledge and training have been identified as significant barriers (Tomacheuski et al., 2020). Regulatory frameworks should be reviewed and updated to ensure that they are fit for purpose and effectively safeguard animal welfare (Pound and Nicol, 2018).

Furthermore, interdisciplinary collaborations between pharmacologists, veterinarians, and researchers should be encouraged to foster the development of innovative solutions for pain management in animal models (Demarco and Nunamaker, 2019; Hutson et al., 2019). By addressing these future directions, the field can move towards more humane and scientifically rigorous practices in oncology research involving animal models.

8 Concluding Remarks

The evaluation of analgesics in oncology research involving animal models has revealed several critical insights. Pain management is essential not only for ethical reasons but also for the validity of scientific data. Unmanaged pain can act as a significant stressor, leading to immune system perturbations and potentially confounding experimental results. However, the use of analgesics, particularly opioids and NSAIDs, can also influence key biological processes such as cell proliferation, apoptosis, and angiogenesis, which are crucial in cancer research. Studies have shown that multimodal analgesic protocols, while effective in reducing pain, may not fully mitigate all distress factors, indicating the need for comprehensive pain and distress management strategies. Additionally, retrospective reviews have highlighted significant gaps in the implementation of effective analgesic regimens, with many studies failing to provide adequate postoperative care.

The findings underscore the dual challenge of managing pain in animal models while ensuring the integrity of oncology research. Effective pain management is crucial for animal welfare and can significantly impact the quality of research data. The variability introduced by both pain and analgesics necessitates a careful balance to optimize both animal welfare and scientific outcomes. The retrospective harm-benefit analysis of pre-clinical studies has revealed that many studies do not meet ethical standards, with severe suffering reported in a significant number of cases. This calls for a review and reform of current regulations and practices to ensure that animal welfare is prioritized without compromising the scientific validity of research.

The ethical considerations in oncology research involving animal models are profound. The need to alleviate pain and distress in animal subjects is not only a legal and moral obligation but also a scientific necessity. The current practices, as revealed by retrospective reviews, indicate a pressing need for improved regulatory frameworks and adherence to guidelines that ensure both animal welfare and the integrity of scientific research. Future research should focus on developing and implementing comprehensive pain management protocols that address both surgical and non-surgical distress factors. Additionally, there should be a concerted effort to educate and train researchers on the importance of pain management and the ethical implications of their work. Balancing the need for scientific rigor with ethical responsibility will be key to advancing oncology research in a humane and scientifically sound manner.

Acknowledgments

AnimalSci Publisher extends its sincere gratitude to the two anonymous peer reviewers for their contributions during the evaluation of this manuscript.

Conflict of Interest Disclosure

The authors affirm that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

References

Bratcher N., Frost D., Hickson J., Huang X., Medina L., Oleksijew A., Ferguson D., and Bolin S., 2019, Effects of buprenorphine in a preclinical orthotopic tumor model of ovarian carcinoma in female CB17 SCID mice, Journal of the American Association for Laboratory Animal Science, 58(5): 610-618.
https://doi.org/10.30802/AALAS-JAALAS-18-000127

Carbone L., 2019, Ethical and IACUC considerations regarding analgesia and pain management in laboratory rodents, Comparative Medicine, 69(6): 443-450.
https://doi.org/10.30802/AALAS-CM-18-000149
PMid:31212034

Carbone L., and Austin J., 2016, Pain and laboratory animals: publication practices for better data reproducibility and better animal welfare, PLoS ONE, 11: e0155001.
https://doi.org/10.1371/journal.pone.0155001

Clutton R., 2018, A review of factors affecting analgesic selection in large animals undergoing translational research, Veterinary Journal, 236: 12-22.
https://doi.org/10.1016/j.tvjl.2018.04.006

DeMarco G.J., and Nunamaker E.A., 2019, A review of the effects of pain and analgesia on immune system function and inflammation: relevance for preclinical studies, Comparative Medicine, 69(6): 520-534.
https://doi.org/10.30802/AALAS-CM-19-000041
PMid:31896019

Garden O., Volk S., Mason N., and Perry J., 2018, Companion animals in comparative oncology: one medicine in action, Veterinary Journal, 240: 6-13.
https://doi.org/10.1016/j.tvjl.2018.08.008
PMid:30314880

Ghodasara P., Satake N., Sadowski P., Kopp S., and Mills P.C., 2022, Investigation of cattle plasma proteome in response to pain and inflammation using next generation proteomics technique, SWATH-MS, Molecular Omics, 18(2): 133-142.
https://doi.org/10.1039/d1mo00354b

Grandhi R.K., and Perona B., 2019, Mechanisms of action by which local anesthetics reduce cancer recurrence: a systematic review, Pain Medicine, 21(2): 401-414.
https://doi.org/10.1093/pm/pnz139
PMid:31209496

Guimarães-Pereira L., 2016, Persistent postoperative pain and the problem of strictly observational research, Pain, 157(5): 1173-1174.
https://doi.org/10.1097/j.pain.0000000000000501

Herrmann K., and Flecknell P., 2019, Retrospective review of anesthetic and analgesic regimens used in animal research proposals, ALTEX, 36(1): 65-80.
https://doi.org/10.14573/altex.1804011
PMid:30421451

Herskin M., and Nielsen B., 2018, Welfare effects of the use of a combination of local anesthesia and nsaid for disbudding analgesia in dairy calves-reviewed across different welfare concerns, Frontiers in Veterinary Science, 5: 117.
https://doi.org/10.3389/fvets.2018.00117
PMid:29951250

Hooijmans C., Draper D., Ergün M., and Scheffer G., 2019, The effect of analgesics on stimulus evoked pain-like behaviour in animal models for chemotherapy induced peripheral neuropathy - a meta-analysis, Scientific Reports, 9: 17764.
https://doi.org/10.1038/s41598-019-54152-8
PMid:31745014

Hooijmans C., Geessink F., Ritskes-Hoitinga M., and Scheffer G., 2015, A systematic review and meta-analysis of the ability of analgesic drugs to reduce metastasis in experimental cancer models, Pain, 156: 1835-1844.
https://doi.org/10.1097/j.pain.0000000000000296
PMid:26172554

Huss M.K., Felt S.A., and Pacharinsak C., 2019, Influence of pain and analgesia on orthopedic and wound-healing models in rats and mice, Comparative Medicine, 69(6): 535-545.
https://doi.org/10.30802/AALAS-CM-19-000013

Hutson C.L., Gallardo-Romero N., Carroll D.S., Salzer J.S., Ayers J.D., Doty J.B., Hughes C.M., Nakazawa Y., Hudson P.N., Patel N., Keckler M.S., Olson V.A., and Nagy T., 2019, Analgesia during monkeypox virus experimental challenge studies in prairie dogs (Cynomys ludovicianus), Journal of the American Association for Laboratory Animal Science (JAALAS), 58(1): 20-29.
https://doi.org/10.30802/AALAS-JAALAS-18-000036

Liu M., Ma J., Li J., Sun J., Zhou H., Guan S., Han Y., Zhang X., and Bian J., 2021, A comparison of the clinical effectiveness between low-dose strong opioids and non-steroidal anti-inflammatory drugs in the treatment of mild cancer pain: a randomized trial, Journal of Pain Research, 14: 3411-3419.
https://doi.org/10.2147/JPR.S322893
PMid:34849358

LeBlanc A., and Mazcko C., 2020, Improving human cancer therapy through the evaluation of pet dogs, Nature Reviews Cancer, 20(12): 727-742.
https://doi.org/10.1038/s41568-020-0297-3
PMid:33159062

Lofgren J., Miller A.L., Lee C.C.S., Bradshaw C., Flecknell P., and Roughan J., 2018, Analgesics promote welfare and sustain tumour growth in orthotopic 4T1 and B16 mouse cancer models, Laboratory Animals, 52(4): 351-364
https://doi.org/10.1177/0023677217749582
PMid:29308688

Martin M.S., Baysinger A., Viscardi A.J., Kleinhenz M.D., Edwards-Callaway L.N., Johnstone E.C., and Coetzee J.F., 2019, Survey of veterinary student attitudes toward animal welfare and pain, American Association of Bovine Practitioners Conference Proceedings, 2019: 218.
https://doi.org/10.1093/jas/skz258.012
PMid:31424550

Paterson E., and Turner P., 2022, Challenges with assessing and treating pain in research primates: a focused survey and literature review, Animals: an Open Access Journal from MDPI, 12: 2304.
https://doi.org/10.3390/ani12172304

Pchelintsev M., 2020, Pain syndrome in oncology: possibilities of dexketoprofen administration, Meditsinskiy sovet = Medical Council, 9: 146-154.
https://doi.org/10.21518/2079-701x-2020-9-146-154

Peterson N., Nunamaker E., and Turner P., 2017, To treat or not to treat: the effects of pain on experimental parameters, Comparative Medicine, 67(6): 469-482.
PMid:29219708

Pound P., and Nicol C., 2018, Retrospective harm-benefit analysis of pre-clinical animal research for six treatment interventions, PLoS ONE, 13: e0193758.
https://doi.org/10.1371/journal.pone.0193758
PMid:29554175

Slingsby L., 2010, Considerations for prospective studies in animal analgesia, Veterinary Surgery: VS, 39(5): 532-534.
https://doi.org/10.1111/j.1532-950X.2010.00717.x
PMid:20456626

Stillman M.W., and Whittaker A.L., 2019, Use and efficacy of analgesic agents in sheep (Ovis aries) used in biomedical research, Journal of the American Association for Laboratory Animal Science: JAALAS, 58(6): 755-766.
https://doi.org/10.30802/AALAS-JAALAS-19-000036
PMid:31693136

Taylor D.K., 2019, Influence of pain and analgesia on cancer research studies, Comparative Medicine, 69(6): 501-509.
https://doi.org/10.30802/AALAS-CM-19-000002
PMid:31693137

Tomacheuski R.M., Taffarel M.O., Ferrante M., and Luna S.P.L., 2020, Preliminary survey of the attitudes of Brazilian scientists towards pain management and assessment in animals used in science, Veterinary Anaesthesia and Analgesia, 47(5): 647-656.
https://doi.org/10.1016/j.vaa.2020.05.007
PMid:32653379

Winder C., Miltenburg C., Sargeant J., LeBlanc S., Haley D., Lissemore K., Godkin M., and Duffield T., 2018, Effects of local anesthetic or systemic analgesia on pain associated with cautery disbudding in calves: a systematic review and meta-analysis, Journal of Dairy Science, 101(6): 5411-5427.
https://doi.org/10.3168/jds.2017-14092
PMid:29656894

Workman P., Aboagye E., Balkwill F., Balmain A., Bruder G., Chaplin D., Double J., Everitt J., Farningham D., Glennie M., Kelland L., Robinson V., Stratford I., Tozer G., Watson S., Wedge S., Eccles S., Navaratnam V., and Ryder S., 2010, Guidelines for the welfare and use of animals in cancer research, British Journal of Cancer, 102: 1555-1577.
https://doi.org/10.1038/sj.bjc.6605642
PMid:20502460

Xu J., Thurston S., Robinson T., Escara-Wilke J., Daignault-Newton S., Martin T., Keller E., and Keller J., 2021, Effects of analgesics on tumor growth in mouse models of prostate cancer bone metastasis, Journal of the American Association for Laboratory Animal Science, 60(5): 529-537.
https://doi.org/10.30802/AALAS-JAALAS-20-000060
PMid:34626416