Pain and analgesia in rabbits: a review.

Abstract

Objective To provide an overview of pain and analgesia in rabbits with the aim of developing a more accurate understanding of these topics. To illustrate and discuss the areas that have advanced in recent years and those that still require further research.

Databases used Three key subject resources were used: Web of Science, Medline and CAB Abstracts. Search terms including rabbits, lagomorphs, laboratory animals, pet, pain, surgical procedures, ovariohysterectomy, orchiectomy, castration, analgesia, opioids, and non-steroidal-anti-inflammatory drugs were included. References from books and articles relevant to the topics were also included.

Conclusions Rabbit medicine has improved over the last 20 years, but the literature suggests that pain management in this species is still inadequate and veterinary professionals believe their knowledge of pain and analgesia in this species is limited. Assessment and quantification of pain in rabbits can be challenging in a clinical environment not only because as prey species rabbits tend to hide signs of pain but also because there are no validated methods to assess pain except the Rabbit Grimace Scale (RbtGS) which is based on only one rabbit breed.

It is the current consensus that peri-operative multimodal analgesia is best practice. However, it is not widely used in rabbits. In rabbits, analgesia protocols and dosages reported in the literature are often poorly researched and do not result in complete pain amelioration with the return of normal behaviour of the rabbit. The present literature on rabbit pain and analgesia presents gaps either due to unexplored areas or insufficient findings. Further research should focus on these areas with the aim of improving the welfare of rabbits within a veterinary clinic.

Keywords rabbit, pain, analgesia, pain assessment, pain amelioration

Introduction

In the United Kingdom (UK), 68% of the pet rabbit population is registered with a veterinary clinic, and it is estimated that circa 600,000 rabbits are neutered every year (PAW-Report 2017). Despite the high number of rabbits undergoing surgical procedures, anaesthesia and analgesia protocols for rabbits are still limited compared to those for cats and dogs (Johnston 2005; Keown et al. 2011). Moreover, rabbit mortality rate (1.39%) is 6 - 8 times higher than cats (0.24%) and dogs (0.17%) respectively (Brodbelt 2009). Uncontrolled and poorly managed perioperative pain, prolonged recovery time and postoperative gastrointestinal ileus are well-recognised causes of mortality in pet rabbits (Longley 2008; Brodbelt 2009; Wenger 2012).

In 1999, a survey on perioperative analgesia in cats and dogs showed that analgesia was not always administered postoperatively, and only a small number of animals received any form of analgesia during routine procedures such as neutering (cats: ovariohysterectomy 26%, castration 16%; dogs: ovariohysterectomy 53%, castration 32 %) (Capner et al. 1999). Similar results were shown in a study of small mammals where only 22% of animals such as rabbits, ferrets, guinea pigs and hamsters undergoing surgical procedures received analgesia (Lascelles et al. 1999).

In recent years, analgesia administration in companion animals such as cats and dogs has increased, and in 2013, 98% of surveyed UK veterinary surgeons reported administering some form of analgesia for routine procedures (Hunt et al. 2015). It is unknown if similar trends have occurred for small mammals such as rabbits. At present, it appears that veterinarians treating rabbits (including those kept in laboratories) are unfamiliar and unsure of available drugs, dosage ranges and the effects of the drugs (Leach et al. 2009; DiVincenti et al. 2016). A recent study showed that there was a poor compliance rate amongst New Zealand veterinarians in using analgesia in small mammals such as rabbits and guinea pigs (Keown et al. 2011). More

than 60% of the respondents felt their knowledge of pain recognition, and analgesia in these two species was inadequate (Keown et al. 2011). This percentage is nearly twice the percentage of veterinarians (30-42%) that doubt their knowledge in recognising pain in cats and dogs (Weber et al. 2012; Beswick et al. 2016).

Assessment and quantification of pain are considered challenging due to differences in the expression of pain across individuals and species and a lack of a 'gold standard' method to assess pain. Moreover, the rabbit as a prey species is evolutionally predisposed to mask signs of pain, making this task even more difficult.

This review will explore what can cause pain in rabbits, concentrating in particular upon the veterinary environment, will give an introduction to how pain can be assessed in rabbits and finally it will describe what is currently available regarding protocols and drugs to ameliorate pain in rabbits while at the clinic.

Three key subject resources were used: Web of Science, Medline and CAB Abstracts. Search terms including rabbits, lagomorphs, laboratory animals, pet, pain, surgical procedures, ovariohysterectomy, orchiectomy, castration, analgesia, opioids, and non-steroidal-anti-inflammatory drugs were included. References from books and articles relevant to the topics were also included. The research will consider references on both laboratory and pet rabbits.

Painful procedures and conditions in rabbits

Pain has been defined by the International Association for the Study of Pain as 'An unpleasant sensory and emotional experience associated with actual or potential tissue damage' (https://www.iasp-pain.org/terminology?navItemNumber=576#Pain). Three studies have attempted to classify veterinary conditions that could lead to pain in rabbits. One study on pet rabbits reported common conditions such as gastrointestinal diseases, fight wounds, neutering and urinary problems to be painful (Rooney et al. 2014). This study had an expert panel rate

levels of suffering associated with each condition but not specifically the severity of pain. A second study instead focused on surgical procedures performed on pet rabbits and the intensity of pain (Keown et al. 2011). Orthopaedic procedures were scored as the most painful procedures, followed by ovariohysterectomy (OVH), castration and surgical treatment of abscesses. Tumour surgical removal and dental treatment were described as less painful procedures (Keown et al. 2011). Similar findings were found in a study on laboratory rabbits; orchiectomy and caesarean section were considered causing mild to moderate pain while major laparotomy and organ incision were suggested to cause moderate to severe pain (Kohn et al. 2007). These studies overall agree with the findings of those reported in other species where, for example, OVH is considered a more painful procedure than orchiectomy reflecting the different complexities of the two surgical procedures.

Pain assessment

The experience of pain is multi-dimensional involving physiological and behavioural changes. These changes can be identified in rabbits experiencing pain and can be used as assessment tools (Kohn et al. 2007). However, pain recognition can be affected by factors such as the individual, age, the subjectivity of the observer etc. Moreover, physiological parameters have a limited function as they can also be altered by positive arousal and concurrent problems such as infections and stress, masking the changes due to pain. In rabbits, an increase in heart and respiratory rate is often seen during handling (Wenger 2012; Varga 2014) while body temperature does not seem to be altered by pain (Cooper et al. 2009). However, a decrease in body weight was a common finding in many studies on rabbit pain and analgesia (Cooper et al. 2009; Leach et al. 2009; Weaver et al. 2010; Goldschlager et al. 2013). It was deduced that this was due to a reduced appetite. Details of research studies reporting pain-related physiological changes in rabbits are summarised in Table 1.

Behavioural changes are considered a more valuable and reliable method to assess pain in rabbits and a return to what is considered normal behaviour for this species is regarded as a reliable indicator that pain is no longer present or that the analgesic treatment is effective (Mayer 2007). In a study of 20 female New Zealand White (NZW) rabbits following OVH, it was found that appetite, faecal output and travelling distance decreased postoperatively in all animals (Weaver et al. 2010). Another study of seven male NZW rabbits following abdominal surgery also noticed a reduction of activity, exploring and appetite postoperatively (Farnworth et al. 2011). The authors also noticed an increase of grooming of the surgical wound area and body flinching (Farnworth et al. 2011). Details of research studies reporting pain-related behaviours of rabbits found in the literature are summarised in Table 1.

Pain scales

Pain scales can be used to carry out a more structured pain evaluation of the animal and allow the intensity of the pain to be quantified: the higher the score, the higher the level of pain that the animal is suffering. This can help the clinician to determine if successful pain management has been achieved or if further analgesia is needed to prevent the animal from suffering.

The first known attempt to quantify pain in laboratory animals such as cats and dogs but also rabbits and rats was made in 1985 (Morton & Griffiths 1985). They used several variables such as body weight, animal appearance, physiological parameters, unprovoked behaviour and behavioural responses to external stimuli to achieve an overall score using a scale from 0 (normal) to 3-4 (severe). To date, there have not been follow-up studies to further develop a composite pain scale for rabbits.

Grimace scales are now popular and use changes in facial expression to quantify pain. They have been developed and validated in several species (Sotocinal et al. 2011; Leach et al. 2012; Dalla Costa et al. 2014; Hageri et al. 2017) and recently also in rabbits as well (Keating et al.

2012). The facial expression of rabbits was evaluated and scored by observers while the rabbits' ears were tattooed with or without the use of local anaesthesia. It was found that some facial features changed depending on the level of the pain. The scale varies from 'Not present' (0) to 'Obviously present' (2) for each action unit and assesses facial changes such as orbital tightening, cheek flattening, nose shape, whisker position and ear position.

Despite the fact that several pain-scoring systems are now available for veterinarians, pain assessment tools are still rarely used. In two recent survey on cats and dogs from UK and Australia, only 17% and 20% of the respondents respectively reported using pain scales (Weber et al. 2012; Hunt et al. 2015). In a review on pain management in laboratory pigs, only one article (1/233) described the use of a pain scoring system (Bradbury et al. 2016). Similarly, little use of pain scales is reported in rabbits (Grint 2013).

Pain amelioration

In a clinical setting, perioperative analgesia is of great importance in order not only to reduce negative effects and complications following a surgical procedure but also to reduce the risks under anaesthesia (Bonnet & Marret 2005). The right analgesic protocol aims to minimise pain and allows the animal to exhibit more normal behaviour, starting the recovery more quickly. Pain can be controlled by both pharmaceutical and non-pharmaceutical approaches. A non-pharmaceutical approach is defined as methods that do not employ drugs, as part of a multimodal approach to pain management (Corti 2014). Techniques such as cold and heat therapy, acupuncture (Parmen et al. 2015) and low-level-laser therapy (LLLT) are anecdotally used in rabbits(Cho et al. 2004). However, too few references have been found in the literature to understand if they can be beneficial in rabbits and they will not be discussed further in this review.

Pain can be prevented and reduced in many ways, and expert opinion is that a multimodal approach, a combination of two or more different types of analgesic drugs administered together, should be considered (Bonnet & Marret 2005). In pet rabbit medicine, multimodal analgesia is advised (Longley 2008; Wenger 2012; Goldschlager et al. 2013). However in a review of 128 papers on the analgesic administration to laboratory rabbits a decade ago, only 48% of the studies reported systemic analgesia agents, and none reported the use of a multimodal approach (Coulter et al. 2011). Buprenorphine alone was used in 60-70% of the studies while non-steroidal anti-inflammatory drugs (NSAIDs) were used only in 20-21%. The authors, however, noticed an increased use of systemic analgesia from 16% to 48% over a 10-year period (Coulter et al. 2011). Further current research is necessary in this field in this species.

Opioids

Opioids are a category of versatile and efficacious drugs that are used to inhibit pain and can be dosed to effect. They are largely used in companion animals for their analgesic and sedative properties as part of the anaesthesia premedication protocol and perioperative analgesia. The side effects of opioid drugs are only seen with overdose; common side effects in rabbits include respiratory depression, bradycardia, hypothermia, drowsiness (Wenger 2012; Varga 2014), decreased arterial blood pressure, increased arterial carbon dioxide and a drop in arterial oxygen tension (Goldschlager et al. 2013). Opioids also have the potential to reduce gastrointestinal motility. However, this does not seem to have clinical relevance in rabbits (Cooper et al. 2009; Goldschlager et al. 2013; Deflers et al. 2018).

For rabbits, the main opioids used and reported in the literature are partial μ agonists such as buprenorphine, agonist-antagonists such as butorphanol and full μ agonists such as fentanyl (Coulter et al. 2009; Wenger 2012; Varga 2014). Morphine, methadone and oxymorphone have

also been used to treat severe acute pain (Barter 2011; Meredith 2015), but little is known about their clinical relevance and effects in rabbits.

Buprenorphine is a partial agonist at the mu receptor and is the most commonly used analgesic drug in rabbits (Coulter et al. 2011). It is administered at a dose of 0.01-0.05 mg kg $^{-1}$ with duration of action of 6-10 hours (Meredith 2015). It can be administered via the intravenous (IV), intramuscular (IM), subcutaneous (SC) and trans-mucosal (OTM) route (Wenger 2012). Intranasal bioavailability of buprenorphine in rabbits has also been assessed with an absorption rate of 10 minutes (mean T_{MAX}) (Lindhardt et al. 2001). The SC and OTM routes are considered less reliable routes with poor absorption in rabbits (Freijs & Kannin 2016). In a study on 24 male NZW rabbits during a three day post-operative period, a dosage of 0.02 mg kg^{-1} buprenorphine every 12 hours given SC resulted in four animals showing moderate to severe pain by the time they were due the next dose (DiVincenti et al. 2016). Another study that tested post-operative analgesia for orthopaedic surgeries in 18 male NZW rabbits suggested that a dose of 0.02-0.05 mg kg $^{-1}$ SC did not provide adequate analgesia (Hedenqvist et al. 2016). The adjunct of carprofen at 5 mg kg $^{-1}$ also did not help to relieve the pain in these rabbits (Hedenqvist et al. 2016). However the combination of buprenorphine (0.01 mg kg $^{-1}$) and meloxicam (0.1 mg kg $^{-1}$) together given SC seemed to mitigate pain in 39 male NZW rabbits during a post-operative period of three days after receiving a vascular cut-down procedure of the femoral artery (Goldschlager et al. 2013). These studies suggest that although a multimodal approach is advisable, the choice of NSAID might also need to be taken into consideration. Moreover, the efficacy of the dose rate related to the severity of the procedure should also be further researched.

Butorphanol is a mu-antagonist and k-agonist opioid suitable for the treatment of mild to moderate pain. It is advised at a dose of 0.1-0.5 mg kg $^{-1}$ (Meredith 2015) and has a duration of action of around 2-4 hours in rabbits (Goldschlager et al. 2013). It can be administered via

the IM and IV route, but it has a longer half-life when given SC (3.2 hours) than IV (1.6 hours) (Varga 2014). Fentanyl is a full mu-agonist and is administered in rabbits in combination with fluanisone, a butyrophenone derivate (Hypnorm) at a combined dose of 0.2-0.3 mL kg^{-1} (Meredith 2015). Hypnorm is licensed for the sedation and anaesthesia in rabbits in the UK, and it can be antagonised by butorphanol and buprenorphine. Transdermal administration of fentanyl in rabbits has also been reported providing analgesia for three days (Foley et al. 2001; Wenger 2012). Another opioid commonly used in rabbits is tramadol. It has low activity at the mu opioid receptor and inhibits noradrenaline and serotonin reuptake (Souza et al. 2008). It is commonly used to treat mild acute and chronic pain due to osteoarthritis and neoplasia (Meredith 2015). In companion animals like cats and dogs, tramadol is administered at a dosage of 1-4 mg kg^{-1} (KuKanich 2013) while in rabbits, it is administered orally (PO) at a dosage of 3-10 mg kg^{-1} (Johnston 2005; Meredith 2015). However, a recent study showed that a dose of 11 mg kg^{-1} did not reach the human therapeutic plasma concentration and a higher dose might be necessary to provide analgesia in this species (Souza et al. 2008). In a study on six female NZW rabbits, 4.4 mg kg^{-1} tramadol administered IV while under anaesthesia using isoflurane vaporised in 100% oxygen caused a decrease in heart rate and arterial blood pressure with a minimal change in the minimum alveolar concentration of isoflurane (Egger et al. 2009).

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs have antipyretic, anti-inflammatory and analgesic activity (Mathews et al. 2014). They are contraindicated in rabbits with hepatic and renal diseases, gastrointestinal ulcerations and conditions with reduced organ perfusion (Johnston 2005).

Commonly reported NSAIDs used in rabbits are carprofen and meloxicam (Barter 2011). Flunixin meglumine and ketoprofen have also been reported to be used in rabbits (Coulter et

al. 2009), but little is known about their efficacy in this species. Use of acetylsalicylic acid and paracetamol has also been reported in rabbits (Varga 2014), but with poor analgesic and anti-inflammatory properties when compared to the other NSAIDs and they are currently rarely administered.

Carprofen is an NSAID with weak cyclo-oxygenase inhibitor properties, and it is used to treat mild to moderate acute and chronic pain. It can be administrated in rabbits IV, SC and PO at a dose of 2-4 mg kg $^{-1}$ (Carpenter 2005; Hawkins 2002). However, no known pharmacokinetic studies have been carried out in rabbits, and the dose rates are untested (Varga 2014). A recent study showed that 5 mg kg $^{-1}$ of carprofen administered to rabbits postoperatively in conjunction with buprenorphine did not reduce the grimace scale pain score when compared to the control group (buprenorphine only) (Hedenqvist et al. 2016).

Meloxicam is a well used and tested NSAIDs in companion animals including rabbits (Turner et al. 2006; Leach et al. 2009; Goldschlager et al. 2013). It can be administered SC, IM and PO. In cats and dogs, it is administered at a loading dose of 0.3 and 0.2 mg kg $^{-1}$ respectively (Ramsey 2014) while in laboratory animals such as rats and mice a dosage of 1-2 mg kg $^{-1}$ is considered necessary to achieve an adequate analgesic effect (Carpenter 2005). In rabbits, the administration is currently advised at a dosage of 0.6 mg kg $^{-1}$ up to 1 mg kg $^{-1}$ (Meredith 2015). A study on ten female NZW rabbits reported that rabbits could be treated with meloxicam at a dose of either 0.3 mg kg $^{-1}$ or 1.5 mg kg $^{-1}$ PO given once a day for five days (Turner et al. 2006). These results were later confirmed and the dosage of 0.2-0.3 mg kg $^{-1}$ once a day was tolerated by eight female NZW rabbits over a period of ten days (Carpenter et al. 2009). In 2013, Fredholm et al. also carried out a study to assess the pharmacokinetics of meloxicam administered PO. It was tested on six NZW rabbits at a dosage of 1 mg kg $^{-1}$ once a day over five days and found to be well-tolerated (Fredholm et al. 2013). These results were later confirmed by Delk et al. (2014), who demonstrated that the administration of 1 mg kg $^{-1}$ of

meloxicam once a day for 29 days was safe in this species, with no obvious side effects detected (Delk et al. 2014). These findings may also suggest that it may be a suitable regimen for the treatment of chronic pain in rabbits. Although, additional trials are required.

A study on 30 Female Dutch belted rabbits undergoing OVH showed that meloxicam at a dosage of 0.2 mg kg $^{-1}$ given SC once a day for two days was comparable to a group receiving buprenorphine (0.03 mg kg $^{-1}$ IM q 12 hours).(Cooper et al. 2009). However, all animals showed decreased food intake, faecal output and weight suggesting that perhaps all animals suffered a degree of discomfort. In 28 female NZW rabbits, a dose of 1 mg kg $^{-1}$ on the day of the surgical procedure followed by 0.5 mg kg $^{-1}$ during the following two days, instead seemed to induce some degree of postoperative analgesia when compared to the control group and the two treatment groups at lower dosages of meloxicam (Leach et al. 2009). In the study on 39 male NZW rabbits receiving a vascular cut-down procedure, a combination of buprenorphine at 0.01 mg kg $^{-1}$ and meloxicam at 0.1 mg kg $^{-1}$ once a day for three days seemed to be more beneficial compared to meloxicam given solely subcutaneously at 0.2 mg kg $^{-1}$ once daily (Goldschlager et al. 2013). These results were based on body weight, food intake and faecal and urinary output. These studies in conjunction with the pharmacokinetic trials suggest that postoperative analgesia in rabbits is yet not fully understood and pain is not adequately treated in this species.

Local anaesthetics

Local anaesthetics are a group of drugs that are sodium channel blockers, and they block the transmission of painful stimulation to the CNS (Johnston 2005). In rabbits, local side effects are associated with potential neurotoxicity during the tissue infiltration (Gozil et al. 2002). In humans and animals, systemic side effects are associated with neurological and cardiovascular signs and systemic hypotension due to accidental intravascular injection (Adam et al. 2011).

Common local anaesthetic drugs used in rabbits are EMLA cream (a eutectic mixture of 2.5% prilocaine and 2.5% lidocaine), and lidocaine and bupivacaine injectable solutions (Wenger 2012). In rabbits, EMLA cream is used for procedures such as ear tattooing (Keating et al. 2012) and placement of intravenous catheters (Varga 2014). Lidocaine (2-4 mg kg^{-1}) and bupivacaine (0.5-1 mg kg^{-1}) are used for local infiltration and, for nerve blocks for dental extraction, intra-testicular administration during castration and epidural analgesia (Wenger 2012; Johnson-Delaney & Harcourt-Brown 2013; Varga 2014). A recent study on laboratory rabbits demonstrated that application of 1 mm thick layer of EMLA cream applied to both inner and outer surface of the pinna 20 minutes before ear tattooing reduced struggling during handling and reduced physiological and behavioural changes associated with pain (Keating et al. 2012). In a veterinary clinic setting, EMLA cream is reported as an effective local anaesthetic to prevent the rabbit from head shaking during venepuncture and insertion of IV catheters (Longley 2008; Varga 2014). Wound infiltration and nerve blocking during dental procedures with lidocaine and bupivacaine reduce the risks of self-trauma and anorexia in rabbits (Varga 2014). A study on 39 male NZW rabbits showed that a single dose of 0.5% bupivacaine given postoperatively at the site of the surgical skin incision gave similar results to the administration of meloxicam alone or buprenorphine alone (Goldschlager et al. 2013). However, it was also noticed that the rabbits in these three groups (bupivacaine, meloxicam and buprenorphine) all had an increase of faecal corticosterone metabolites and a reduction of body weight during the first seven days postoperatively, suggesting that the rabbits experienced stress or pain despite the analgesic treatments (Goldschlager et al. 2013).

In two recent surveys, in Australia and the UK, investigating the veterinarians' perception of pain in cats and dogs it was found that none (Weber et al. 2012) or few (Hunt et al. 2015) of the respondents used local anaesthetic drugs with members of the Association of Veterinary Anaesthetists being more likely to use local anaesthetic drugs (Hunt et al. 2015). This would

suggest that more research and education might be necessary to incorporate local anaesthetics within an analgesic protocol.

Discussion

This review provides an overview of the relevant literature published over the last 20 years on rabbit pain assessment and quantification and the efficacy of analgesic drugs in this species. The study populations in many of the scientific papers comprise laboratory rabbits rather than pet rabbits. This does not come as a surprise as rabbits are widely used as experimental models in both human and animal research. However, pet and laboratory rabbit populations can be very different from a demographic and management point of view. While the pet rabbit population presents several breeds with different body sizes and types, more akin to the cat and dog population, the laboratory rabbit population is often limited to fewer breeds such as the NZW, and Dutched Belted rabbits, kept in standardised conditions. Laboratory rabbits are young and healthy, and therefore the research findings rarely take into consideration the differences in age and potential concurrent health problems, that are more likely to be found in pet rabbits. Moreover, although pain relief must be provided to laboratory rabbits undergoing painful procedures (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32010L0063), the choice of the analgesic drug may be dictated also by the need of preventing side effects and complications that could interfere with the study's findings rather than the complete return to the animal's normal behaviour (Carbone & Austin 2016; Hedenqvist et al. 2016). For these reasons, studies on analgesia reported in laboratory rabbits might not be suitable for pet rabbits and the types of surgical procedures that are commonly performed in veterinary clinics. However, during this review, it was noticed that in the last few years, more studies have been designed with the pet rabbit in mind or using a

pet rabbit population. This suggests an increased interest in these pets and the acknowledgement of their specific needs.

During the review of the literature published on pain assessment, three studies were found on laboratory rabbits (Leach et al. 2009; Weaver et al. 2010; Farnworth et al. 2011) and none on pet rabbits. All three studies aimed to identify the behavioural response to pain to optimise postoperative analgesia. Ethograms of rabbit behaviours observed during the studies were developed. One study (Leach et al. 2009) found that behaviours such as twitch, wince and staggering grouped as "Inactive pain behaviour" were the most indicative indicators of pain. Weaver et al. (2010) instead reported that a reduction in activity was a better indicator of pain while Farnworth et al. (2011) concluded that a decline in those behaviours that are commonly expressed such as eating and exploring, may be a more effective way of assessing postoperative pain. Although the three studies do not agree, they all describe potential behaviours that rabbits may express while experiencing pain. It is the general consensus that the use of behavioural indicators can be very subjective, and that it relies not only on the knowledge of the species and the individual studied but also on the experience of the observer (Kohn et al. 2007).

Recently the Rabbit Grimace Scale (RbtGS) has been validated as an effective method to assess acute pain in laboratory rabbits. The main advantage of the RbtGS is that is based on only five action units that makes it more accurate and less time-consuming than assessing several behavioural indicators. The main limitation is that it is based on only one breed of rabbit: New Zealand White. Although, in a laboratory context this would not be a problem, in a veterinary clinic it would limit its use as many rabbit breeds with different types of ears and face shapes are generally presented. A way to bypass these limitations could be to perform a 'preoperative' pain assessment once the rabbit is admitted to the hospital. This would emphasise those behaviours and anatomical features specific to the individual rabbit and that might not necessarily change due to pain. However, a more objective approach such as a

multidimensional composite pain scale specific for this species and validated for several breeds of rabbits would overall improve the pain recognition and the use of analgesia. The characteristics of a composite scale are that it should be reliable, repetitive and easy to use (Mathews et al. 2014). Moreover, it should quantify pain allowing a more accurate rescue analgesia intervention. A composite scale for laboratory animals, including rabbits, was developed in 1985 (Morton & Griffiths 1985). This scale was then used as guideline for the development of validated composite scales in other animals but not in rabbits leaving a gap regarding pain assessment in this species.

The management of pain in rabbits is difficult for several reasons. Without a validated pain assessment tool, it is challenging to properly assess if an analgesic drug is effective. Moreover, drugs used to treat rabbits in veterinary clinics are broadly untested with only few papers published. Amongst NSAIDs, meloxicam is one of the most commonly used drugs in rabbits, and several published studies have been found during this literature review. Four papers were found on the pharmacokinetics alone. Two studies concluded that a dosage 3 to 8 times higher than 0.2 – 0.3 mg kg^{-1} may be required in rabbits (Turner et al. 2006; Carpenter et al. 2009). Two later studies confirmed that 1 mg kg^{-1} was necessary to achieve a clinically effective concentration (Fredholm et al. 2013; Delk et al. 2014). Leach et al. (2009) clinically assessed meloxicam at dosages of 0.2, 0.6 and 1 mg kg^{-1} followed 24 hours later respectively by 0.1, 0.3 and 0.5 mg kg^{-1} in 28 NZW rabbits undergoing OVH. The authors concluded that these three dosages were still not adequate to completely treat pain in rabbits undergoing OHV but that the two higher dosages (0.6 and 1 mg kg^{-1}) were more effective in controlling pain than the lower one at 0.2 mg kg^{-1}. This was later confirmed by Goldschlarger et al. (2013) who demonstrated that 0.2 mg kg^{-1} did not have any analgesic benefits. That study also assessed a multimodal analgesic approach and demonstrated that a combination of buprenorphine at 0.01 mg kg^{-1} and meloxicam at 0.1 mg kg^{-1} administered SC daily was more effective than

meloxicam or buprenorphine administered alone. Although it might be difficult to compare these studies as the methodologies are often significantly different, they all demonstarted that meloxicam should be given in rabbits at higher dosages than in cats and dogs. The study by Goldschlarher et al. (2013) also demonstrated the benificial effects of a multimodal analgesic approach in rabbits. Multimodal analgesia in rabbits is recommended in many books, articles and conference proceedings on rabbit pain and analgesia. However little is reported on effective combinations with the return of what would be considered a normal behaviour in this species. Multimodal analgesia is still a largely underresearched field in rabbits.

Conclusions

The literature reported presents gaps due to either unexplored areas or insufficient findings. This review suggests there have been advances in research in order to better understand pain assessment and management in pet rabbits. Assessment and quantification of pain in this species can be challenging in a clinical environment; not only do rabbits tend to hide clinic signs of pain, but the lack of a multidimensional composite pain scale can limit assessment of their pain and effectiveness of the analgesia provided. The Rabbit Grimace Scale (RbtGS) is a valuable tool but may have a limited use in a veterinary setting where many different rabbit breeds are commonly seen.

Many analgesic drugs used in companion animals such as cats and dogs have not been tested on rabbits restricting their use in this species. Many are anecdotally reported, and only few analgesic protocols are supported by research studies that demonstrate a complete pain amelioration with the return of normal behaviour of the rabbit.

Further research should focus on these areas with the aim of improving the welfare of rabbits.

Table 1 Details of physiological and behavioural changes reported in scientific studies on rabbit pain and analgesia

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