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The cardiopulmonary effects and quality of anesthesia after induction with alfaxalone in 2-hydroxypropyl-β-cyclodextrin in dogs and cats: A Systematic Review

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Disclamier

Dr. Whittem is a former employee of and currently serves as a consultant for Jurox Pty Ltd (Rutherford, NSW, Australia) which manufactures the product that is the subject of this study.

The protocol planning, search strategies, choice of problem/population, intervention, comparison and outcome (PICO) questions and manuscript preparation were conducted collaboratively by both authors (KWC and TW). However, because of the acknowledged association of TW with the product sponsor, and because 6/22 (27%) papers included in the study were co-authored by TW, to avoid investigator bias all exclusion of found references and all assessments of level of evidence (LOE), risk of bias (ROB) and strength of evidence were conducted solely by KWC and verified by SAR without input from TW.

Abstract

Objectives

To systematically review the quality of evidence comparing the cardiopulmonary effects and quality of anesthesia after induction with alfaxalone versus other anesthetic agents in dogs and cats.

Data Sources

Studies published from 2001 until 20th May 2013 were identified with the terms 'Alfaxan' OR 'alfaxalone' OR 'alphaxalone' in electronic databases: Discovery, Pubmed, ScienceDirect and Wiley Interscience. The study design and risk of bias of all included studies were assessed.

Data Synthesis

Twenty two studies from 408 (22/408, 5.39%) satisfied the inclusion criteria. Thirteen studies (14/22, 64%) focused on dogs and seven (9/22, 40%) on cats. One study had both dogs and cats as subjects. [1] Twelve studies were rated an LOE1 and six of these as ROB1. One, seven and two studies were rated as LOE2, LOE3, and LOE5 respectively.

Conclusions

In dogs, strong evidence shows that induction quality with either alfaxalone-HPCD or propofol is smooth. Moderate evidence supports this finding in cats. In dogs, moderate evidence shows that there is no significant change in heart rate after induction with either alfaxalone-HPCD or propofol. In cats, moderate evidence shows no significant difference in post-induction

respiratory rate between alfaxalone-HPCD and propofol induction. Strong evidence shows dogs and cats have smooth recoveries after induction using either alfaxalone-HPCD or propofol, before reaching sternal recumbency.

(200 words)

Abbreviations

CHFSROF	Cochrane Handbook of Systemic Reviews of Interventions
CRI	Continuous rate infusion
HPCD	2-hydroxypropyl-β-cyclodextrin
HR	Heart rate
LOE	Level of evidence
PICO	problem/population, intervention, comparison and outcome
RCT	Randomized control trial
ROB	Risk of bias
RR	Respiratory rate
SAP	Systolic arterial pressure
SDS	Simple descriptive scale
VAS	Visual Analogue Scale

Introduction

Rationale

Alfaxalone (3α-hydroxy-5α-pregnane-11,20-dione) is a synthetic neuroactive steroid that enhances and modulates the inhibitory effects of gamma amino butyric acid at the gamma amino butyric acid type A receptors within the central nervous system. Through this mechanism, alfaxalone yields a state of anesthesia that provides good muscle relaxation. In 1971, alfaxalone co-formulated with alfadolone was combined in a polyethoxylated castor oil-based surfactant. Alfadolone was included due to its putative anesthetic and anti-nociceptive effect. It was also assumed that alfadolone would increase the solubility of alfaxalone. [2] Marketed as Saffan® (Schering Plough Animal Health, Union, NJ, USA) for use in animals, the preparation was suggested to have the potential to produce superior hypnosis and anesthesia compared to other injectable anesthetics in use at the time e.g., propanadid, pentobarbital, thiopental, ketamine and xylazine.[2-5]

However, the polyethoxylated castor oil caused adverse effects in both dogs and cats. In dogs, anaphylactic reaction was observed.[6] In cats, injected animals had hyperemia or edema of the pinae or forepaws.[7] Hypotension, hypersensitivity to touch and hyper-reflexia were also noted.[5] Alfaxalone has since been reformulated by solubilizing in 2-hydroxypropyl-β-cyclodextrin (HPCD), which does not lead to histamine release and increases the solubility of alfaxalone by 375 times.[8] Alfaxalone-HPCD is marketed as a clear and colorless solution for induction and maintenance of anesthesia in dogs and cats in Australia, New Zealand, South Africa, the United Kingdom and elsewhere. In September 2012, alfaxalone-HPCD was approved in the United States by the Food and Drug Administration, for induction and maintenance of anesthesia dogs and cats.[9] Studies have been undertaken to evaluate the cardiopulmonary effects and anesthetic quality of this new formulation of alfaxalone, when used for induction and maintenance of anesthesia. The cardiopulmonary effects, quality of induction and recovery of alfaxalone-HPCD in dogs and cats were compared with other anesthetic agents, which includes propofol, etomidate and diazepam/fentanyl induction.[10-22] The quality of anesthesia produced by was assessed in healthy, debilitated and young patients.[11, 17, 20, 23-25] Trials have also been carried out to assess the possibility of using the agent in the anesthesia of other animals, including horses, sheep, goldfish, crocodiles and pigs.[26-33]

To the authors' knowledge, this study is the first systematic review of the peer-reviewed literature for this formulation of alfaxalone-HPCD.[a] This study examines the evidence describing

the quality of induction of anesthesia and recovery from anesthesia, and the post-induction cardiopulmonary effects of alfaxalone-HPCD in dogs and cats compared with other available anesthetic agents.

Objective

To compare the quality of induction and recovery, post induction heart rate (HR), systolic arterial pressure (SAP), respiratory rate (RR) after intravenous alfaxalone-2-hydroxypropyl-β-cyclodextrin (HPCD) anesthetic induction with other induction agents in dogs and cats. The objective of this review was formulated as problem/population, intervention, comparison and outcome (PICO) questions in order to have a more evidence based approach to answering the clinical questions. [34] In canine/feline patients (P), does alfaxalone –HPCD (I) versus other anesthetic agents (C), give a smoother and faster induction (O)? In canine/feline patients (P), is alfaxalone –HPCD (I) versus other anesthetic agents (C), a superior induction agent in terms of preservation of HR and SAP after induction (O)? In canine/feline patients (P), is alfaxalone –HPCD (I) versus other anesthetic agents (C), a superior induction agent in terms of preservation of RR parameters after induction (O)? [34] In canine/feline patients (P), does alfaxalone –HPCD (I) versus other anesthetic agents (C), give a smoother and faster recovery (O)?

Methods

Protocol

A protocol was developed in advance of the study. The protocol specified the eligibility criteria, research questions, data source, search strategy, data collection and extraction process. The method of assessing the risk of bias (ROB) and level of evidence (LOE) were also outlined in the protocol.

Eligibility criteria

Types of studies Since the alfaxalone-HPCD formulation[a] was first marketed in 2001, the review only included studies published from 2001 until 30 May 2013. Included studies were all published in peer-reviewed journals written in English. The types of studies included were: randomized control trials (RCT), prospective clinical trials, four-way crossover experimental

studies, two period crossover experimental studies, prospective experimental studies and prospective single-center observation studies.

Types of participants The study populations included canine and feline patients of all ages anesthetized using the commercial formulation[a] of alfaxalone-HPCD. Both healthy and debilitated patients were included in the study.

Types of intervention: This review included studies which used alfaxalone-HPCD as an anesthetic induction agent by intravenous bolus injection only. Studies with or without any type of premedication were included. Studies that did not identify the formulation of alfaxalone used were excluded in the review.

Types of outcome measures: The outcomes of interest included quality of induction and recovery, by objective or subjective measures. Additional outcome measures were the cardiopulmonary effects of alfaxalone-HPCD evaluated by the post-induction HR, SAP, RR and the incidence of post-induction apnea. The cardiopulmonary effects during maintenance of anesthesia were not examined in this review because these parameters are very dependent on the procedure performed, type of maintenance anesthesia used and the intraoperative adjustment of anesthetic.

Information sources and Search strategy

A board bibliographic search was performed in electronic data bases from 2001 to 30 May 2013. The studies were searched in Discovery, Pubmed, ScienceDirect and Wiley Interscience with the following search terms : “alfaxan OR alfaxalone OR alphaxalone” in any field.

Selection of studies and data extraction

The studies were selected according to the pre-defined eligibility criteria by KWC and were verified by AW. Information was extracted by KWC using a customized data collection sheet

developed. The accuracy and completeness of the extracted data was verified by JLD. When disagreements between authors occurred, they were resolved by consensus. The following were the data items extracted: species and number of subjects, type of study, risk of bias, quality of induction and recovery, post-induction HR, SAP, RR and incidence of apnea.

Risk of bias and study design in individual studies

Level of Evidence (LOE) The articles that matched the inclusion criteria were reviewed and assigned an LOE. The LOE of each study was rated according to the study design by KWC and was verified by SAR to ensure its validity. The LOE was determined according to a pre-designed set of criteria adapted from Reassessment Campaign on Veterinary Resuscitation, which was rated according to the study design.[35] The rating of LOE1 included RCT or meta-analyses of RCT in target species. These include prospective clinical studies with random allocation to intervention or control groups; or meta-analysis of these studies. The rating of LOE2 included prospective clinical studies in target species using concurrent controls (i.e. controls recruited at the same time as experimental subjects) without randomization. These studies were either interventional or observational clinical studies. The rating of LOE3 included experimental laboratory studies in the target species. The rating of LOE4 included clinical retrospective studies in the target species. The rating of LOE5 included case series and case reports in the target species or a single group of animals exposed to intervention without a control group.

Risk of bias (ROB) The rating addresses the risk of bias categorized by the Cochrane Handbook of Systemic Reviews of Interventions (CHFSROF). The risk of bias grading (ROB1, ROB2, ROB3 or ROB4) were then assigned by KWC and verified by SAR. Disagreements between authors were resolved by consensus. ROB1 indicates a very low risk of bias and ROB4 indicates a high risk of bias. [34] A rating of ROB1 indicated the study had adequately addressed the issues of bias relating to the methodology and analysis of data based on the CHFSROF.[34] A rating of ROB2 and ROB3 indicated that one category or two categories of bias were identified in the study respectively. A rating of ROB4 was assigned if three or more categories of bias were identified in the study.

Synthesis of results

Strength of evidence The strength of the entire body of evidence answering the PICO questions was represented by four ranking levels - strong, moderate and weak strength of evidence and insufficient evidence. These rankings represent the amount of evidence that existed in this review. The LOE and ROB assigned to the study were reflected in these rankings. "Strong evidence" was assigned if a specific finding that was reported by at least one LOE1; ROB1 study along with one or more studies included in this review. No contradicting evidence should be found in the included studies. "Moderate evidence" was based on a specific finding that was reported in at least one LOE1 study of any risk of bias grading along with one or more studies included in this review. No contradicting evidence should be found in the included studies. A finding reported by only one LOE1; ROB1 study without other contradicting evidence included in the review was also placed in this category. "Weak evidence" was based on a finding that was reported in more than one LOE2 or LOE3 study included in this review. Findings reported by one LOE1 and either ROB2, ROB3, ROB4 study without contradicting evidence included in the review were also placed in this category. "Insufficient evidence" indicates that there were not enough high quality studies that support the claim or contradicting evidence exists in the included studies. The strength of evidence was assigned by KWC according to the pre-defined criteria and was verified by SAR. Disagreements between authors were resolved by consensus.

Results

Study selection

The process of the literature search and selection is shown in Figure 1. The literature search resulted in a return of 667 records. After removal of duplicates 408 records were screened. Excluded records numbered 379/408 (93%). The remaining 27 full-text articles were assessed for eligibility and 22/29 (76%) studies were eligible for review.

Study characteristics and risk of bias within studies

Characteristics of the studies included in this review are shown in Table 1. Summary of the number of studies assigned to each LOE and risk of bias grading is shown in Figures 2 and 3.

Several categories of bias were identified in the studies included in this review. Many of the studies were not blinded, which increases the risk of detection bias.[10, 13, 14, 24, 25, 36] Some studies had selection bias due to non-random allocation of subjects into treatment groups.[16, 36, 37] Psatha *et al* (2011) had missing data 20 minutes post-induction, which may risk attrition bias.[11] In certain studies, subjects were excluded because of health[12, 37, 38] and ethical reasons[18, 23], death[25] and inadequate sedation[20]. These exclusions would not systematically affect the outcome data and, therefore, would not risk attrition bias. Some of the studies also did not include control groups, which made it difficult to assess the significance of data collected.[24, 25] Studies funded by pharmaceutical companies had ROB downgraded. This was based on multiple peer-reviewed studies, including a systematic review, which have shown research funded by drug companies tend to have outcomes favoring the sponsor. [39-43] It was also shown that the pharmaceutical industry tends to discourage publication of negative studies that it has funded. [44-46] Based on CHFSROF, this leads to bias. [34] No studies were found to have performance and reporting bias in the studies reviewed.

Synthesis of results

Some of the studies included in this review did not compare alfaxalone-HPCD with another induction agent, but reported the outcome parameters of interest.[14, 23, 25, 37, 38, 47-49] These studies were included in this review to provide confirmative evidence. Nevertheless, the strength of evidence supporting a specific claim was based only on studies that compared alfaxalone-HPCD with another induction agent. Some studies did not report the significance of the change in the cardiopulmonary parameter of interest, which made the evaluation process difficult. [12, 17, 49] Most studies compared alfaxalone-HPCD with propofol. Etomidate[16] and fentanyl/diazepam/propofol[11] induction were the other anesthetic agents that were compared, but each of these agents was only evaluated in one study.

Quality of induction There were 11 studies in dogs and three studies in cats that had information on the quality of induction after intravenous injection of alfaxalone-HPCD in dogs. Two of the studies[18, 38] in dogs and one study[17] in cats were rated an LOE1; ROB1. There were a total of six LOE1 studies[11],[13], [14], [18],[20], [38], four LOE3 studies[16], [21], [48], [36] and one LOE5 study[24] in dogs on this subject. One LOE1 study[17], one LOE3

study[23], and one LOE5 study[25] included information on this topic in cats. A total of 322 dogs and 135 cats participated in these studies.

Post-induction cardiovascular effects Eight studies in dogs and five studies in cats investigated the cardiovascular effects after intravenous injection of alfaxalone-HPCD. Among these studies, one study in dogs[20] and another one in cats[17] were rated an LOE1; ROB1. A total of three LOE1 studies[11], [13], [20], four LOE3 studies[16], [21], [48], [36] and one LOE5 study[24] included information on this subject dogs. Two LOE1 studies[12], [17], two LOE3 studies[23], [49] and one LOE5 study[25] included information on this topic in cats. The total number of animals was 169 dogs and 173 cats.

Post-induction respiratory effects Ten studies in dogs and six studies in cats evaluated the respiratory effects after intravenous injection of alfaxalone-HPCD. One of these studies in dogs[20] and one in cats[17] were each graded an LOE1; ROB1. Relevant information was found on post anesthetic induction respiratory effects. For dogs a total of four LOE1 studies[11], [13], [20], [38], five LOE3 studies [10], [16], [21], [48], [36] and one LOE5 study[24] was found. For cats in two LOE1 studies[12], [17], one LOE2 study[37], two LOE3 studies[23], [49] and one LOE5 study[25] in cats . A total of 260 dogs and 208 cats participated in these studies.

Quality of Recovery There were 12 studies in dogs and six studies in cats that had information on the quality of recovery from anesthesia after intravenous injection of alfaxalone-HPCD. One study in dogs [15]and one study[17] in cats were graded an LOE1; ROB1. For dogs there were a total of six LOE1 studies[11], [13], [20], [38] , [1, 47] five LOE3 studies[10], [16], [21], [48], [36] and one LOE5 study[24] on the quality of recovery from anesthesia. For cats there were two LOE1 studies[12], [17], one LOE2 study[37], two LOE3 studies[23], [49] and one LOE5 study[25] on this topic. A total of 235 dogs and 318 cats participated in these studies.

Discussion

Summary of Evidence

In canine patients (P), does alfaxalone –HPCD (I) versus other anesthetic agents (C) , give a smoother and faster induction (O)? Moderate evidence showed that propofol lipid-free emulsion administration tend to have a higher rate of excitation post-induction compared with alfaxalone-HPCD (p = 0.0003, odds ratio 4.5 [1.86 – 10.90]).[18] Otherwise, strong evidence showed the

induction quality of propofol and alfaxalone-HPCD has no significant difference after slow injection (40 – 60 seconds).[13, 18, 21] This finding was supported by one LOE1; ROB1[18] and one LOE1; ROB2 [13]study and one LOE3;ROB1 [21] study. Michou *et al* (2012) (LOE1; ROB1) reported that three (3/30; 10%) dogs in the alfaxalone-HPCD groups were reported to display excitation after induction, whereas six (6/30; 20%) and seven (7/30; 23%) dogs in the propofol lipid macroemulsion group and propofol lipid-free microemulsion[c] group respectively, displayed excitation.[18] The statistical comparison between the three groups of the number of dogs showing these excitatory signs was not reported. The most frequent excitatory phenomena observed were muscle twitching and fasciculation. It should be noted that this may be a formulation effect not necessarily a propofol effect. Propofol lipid-free emulsion has been removed from the market. Moderate evidence showed that propofol lipid-free microemulsionwasassociated with clinical relevant moderate to severe pain behavior during induction while alfaxalone-HPCDwasnot (p = 0.0003, odds ratio 4.5).[18] Moderate evidence showed no significant difference between alfaxalone-HPCD and propofol induction after rapid intravenous injection (<5s) of the agents (p = 0.498). [20] Weak evidence showed that alfaxalone-HPCD has a high quality of induction without significant difference than that of fentanyl/diazepam/propofol induction in dogs of poor anesthetic risks (p = 0.113).[11] There was insufficient evidence to make any conclusions when comparing the induction quality of alfaxalone-HPCD to that of etomidate because it was investigated by only one LOE3; ROB2 study.[16] Maddern *et al* (2010) (LOE1; ROB1) reported the only study with some mild coughing during intubation after alfaxalone-HPCD induction. This study did not compare alfaxalone-HPCD with other agents. This study used an average dose of 1.2 ± 0.4 mg kg^{-1}, which was lower than the dose used reported by other studies and had an average induction time of 184 ± 57 s.[14, 15, 48] The lower dose of alfaxalone used may have contributed to the mild coughing during intubation. Other studies reported that after induction of anesthesia with alfaxalone-HPCD the overall intubation was quiet and uneventful [48] (LOE3; ROB2) and acceptable[24] (LOE5 ; ROB3). Quality of intubation compared with other agents requires further research.

In feline patients (P), does alfaxalone –HPCD (I) versus other anesthetic agents (C), give a smoother and faster induction (O)? Moderate evidence showed that the induction quality of alfaxalone-HPCD was smooth, but not significantly different from that of propofol.[17] Mathis *et al* (2012) (LOE1; ROB1) compared the induction quality between alfaxalone-HPCD and

propofol and reported no significant difference between the two groups (p = 0.813).[17] Most patients in both alfaxalone-HPCD and propofol groups had a very smooth or smooth induction. This findingwassupported by Muir *et al* (2009) (LOE 3; ROB2), who studied the induction quality of alfaxalone-HPCD without comparing with other agents.[23] O'Hagan *et al* (2012) (LOE5; ROB3) studied the quality of induction in feline patients <12 weeks of age and had similar results. [25]

In canine patients (P),is alfaxalone –HPCD (I) versus other anesthetic agents (C), a superior induction agent in terms of preservation of HR and SAP after induction (O)? Moderate evidence showed that therewasno significant change in heart rate after induction of anesthesia with alfaxalone-HPCD, a finding which was not significantly different when compared to propofol.[13, 36] Studies by Suarez *et al* (2012) (LOE1; ROB2), Maney *et al* (2013) (LOE3; ROB1) and Ambros *et al* (2008) (LOE3; ROB4) supported this finding. [13, 21, 36] Both Suarez *et al* (2012) and Ambros *et al* (2008) used anesthetic induction followed by continuous rate infusion (CRI) for anesthetic maintenance, whereas Maney *et al* (2013) used no maintenance anesthesia. [13, 21, 36] There was insufficient evidence to compare the preservation of heart rate after rapid intravenous injection of propofol and alfaxalone-HPCD. [20] Amengual *et al* (2013) (LOE 1; ROB1) reported that the heart rate increased in the alfaxalone-HPCD group (14 ± 33 beats minute^{-1}) and decreased in propofol group (-2 ± 28 beats minute^{-1}). These changes were statistically significant. However, the heart rate was already significantly different between groups after premedication. [20] Further investigation is required to demonstrate the changes in heart rate after rapid injection of alfaxalone-HPCD compared with propofol. Weak evidence showed that alfaxalone-HPCD preserves the heart rate without significant difference from fentanyl/diazepam/propofol induction in dogs of poor anesthetic risks (p = 0.11). [11] No significant change in heart rate was detected after induction by either agent. [11] There was insufficient evidence to compare preservation of heart rate between etomidate and alfaxalone-HPCD.[16] The only study that compared alfaxalone-HPCD with etomidate (LOE3; ROB2) showed a short lived significant increase in heart rate in the alfaxalone-HPCD group and a non-significant reduction in the etomidate group. However, the mean dose rate of alfaxalone-HPCD used in this study was 4.15 mg kg^{-1}, which is twice the recommended dose rate (2 mg kg^{-1}) for unpremedicated dogs. [16] Since a supraclincial dose was used, further studies with a higher LOE are required to compare the preservation of heart rate after alfaxalone-HPCD and etomidate

anesthetic induction . When alfaxalone-HPCD was evaluated without comparing with another induction agent, all studies showed that the agent preserves heart rate. When premedications were being compared for induction of anesthesia with alfaxalone-HPCD, both acepromazine and dexmedetomidine premedication caused no significant change in heart rate after administration of alfaxalone-HPCD (LOE1; ROB2).[14] Muir *et al* (2008) (LOE3; ROB2) and O'Hagan *et al* (2012) (LOE5; ROB3) also reported no significant change in heart rate after induction of anesthesia with alfaxalone-HPCD.[24, 48] All studies reported an increased heart rate after induction of anesthesia with alfaxalone-HPCD and a drop in heart rate after administration of propofol.

Moderate evidence showed a significant drop in both SAP and diastolic arterial pressure (DAP) after rapid intravenous injection (<5 seconds) of propofol or alfaxalone-HPCD. Amengual *et al* (2013) (LOE1; ROB1) reported that both propofol and alfaxalone-HPCD resulted in significant reduction in SAP and diastolic arterial pressure after rapid injection.[20] Dogs in the alfaxalone-HPCD group trended to a higher overall SAP but this did not achieve statistical significance from the propofol group ($p = 0.053$). It is noteworthy that the pre-study Power calculation determined that 30 dogs were needed per group, but because of one exclusion the alfaxalone-HPCD group only achieved 29 cases. Weak evidence showed that SAP was well preserved after slow injection (injecting over 40 – 60 seconds) of alfaxalone-HPCD without significant difference from that of propofol.[21, 36] Both Ambros *et al* (2008) (LOE3; ROB4) and Maney *et al* (2013) (LOE3; ROB1) reported no significant drop in SAP after induction by either agent and the values were not significantly different from one another. [21, 36] Weak evidence showed good preservation of SAP after induction of anesthesia using either alfaxalone-HPCD or fentanyl/diazepam/propofol in patients of poor anesthetic risk.[11] Post-induction SAPs with either of the two protocols were not significantly different from each other ($p = 0.307$) and had no significant difference from baseline (LOE1 ; ROB2).[11]

In feline patients (P), is alfaxalone-HPCD (I) versus other anesthetic agents (C), a superior induction agent in terms of preservation of cardiovascular parameters after induction (O)?
There was insufficient evidence to determine the preservation of heart rate when comparing propofol with alfaxalone-HPCD. Two LOE1 studies (LOE 1; ROB1 and LOE1; ROB2) compared post-induction heart rate between propofol and alfaxan [12, 17]. However, the

significance of the decrease was not assessed. [12, 17]There was also insufficient evidence to deduce the preservation of SAP when comparing alfaxalone-HPCD and propofol induction. The SAP of both groups decreased in the one available study (LOE 1; ROB1) and the overall mean SAP throughout the procedure was not significantly different between groups. [11] The comparison of the post-induction SAP between the two agents was not mentioned. [11] When the post induction heart rate and SAP of alfaxalone-HPCD was investigated without comparison to other agents, LOE 3 and LOE 5 studies reported either no significant change in either parameter or the significance of change was not assessed. [23, 25, 49]

In canine, patients (P), is alfaxalone –HPCD (I) versus other anesthetic agents (C), a superior induction agent in terms of preservation of RR after induction (O)? Weak evidence supports there being no significant respiratory depression after induction of anesthesia with either fentanyl/diazepam/propofol or alfaxalone-HPCD and the change in respiratory rate was not significantly different between these two anesthetic protocols ($p = 0.366$).[11] There was insufficient evidence to determine changes in the respiratory rate after induction of anesthesia when alfaxalone-HPCD and propofol were compared, particularly because of contradictory evidence which derives from studies of different design. Suarez *et al* (2012) (LOE1; ROB2) reported a statistically significant decrease in respiratory rate in both alfaxalone-HPCD group and propofol group, however, the premedication protocol of acepromazine (0.01 mg kg^{-1}) and morphine (0.4 mg kg^{-1}) potentially obscured the effect of the anesthetic protocols.[13] Maney *et al* (2013) (LOE3; ROB2) reported statistically significant respiratory depression in the alfaxalone-HPCD group at one of two time points, whereas their propofol group had a decrease in respiratory rate which did not reach statistical significance. However, the degree of respiratory rate reduction was exactly 50% for each group; alfaxalone-HPCD respiratory rate decreased from baseline of 66 to post-induction of 33 breaths per min (50%) while for propofol respiratory rate decreased from baseline of 62 to post-induction of 31 breaths per min (50%). The within-group variance at baseline of respiratory rate was greater in the propofol group (CV=59.7%) than the alfaxalone-HPCD group (CV=47.0%), possibly accounting for the lack of statistical difference in the propofol group. [21] The dose of alfaxalone-HPCD used in the study by Maney *et al* (2013) (2.6 ± 0.4 mg kg^{-1}) exceeded the manufacturer's recommended induction dose of 2.0 mg kg^{-1} by 30% compared with that used by Suarez et al (1.9 ± 0.007 mg kg^{-1}) which was 5% lower than the target labeled dose.[13, 21] Ambros *et al* (2008) reported in dogs which had

been premedicated with both acepromazine and hydromorphone a decrease in respiratory rate in both alfaxalone-HPCD and propofol groups, which achieved statistical significance only in the propofol group at only two of seven post-dose time points.[36] It should be noted that CRI was used as maintenance anesthesia in all the studies that compared the post-induction respiratory rate in propofol and alfaxalone-HPCD. [13, 21, 36] There was insufficient evidence to compare the immediate post-induction respiratory rate depression between etomidate and alfaxalone-HPCD. The only study (LOE3; ROB2) that compared the two agents reported significant decrease in respiratory rate in both groups. [16] Studies that investigated the post-induction respiratory rate for alfaxalone-HPCD had inconsistent results. The respiratory rate of canine neutering patients of <12 weeks old did not drop significantly (LOE5; ROB4). [24] Two studies (both LOE3; ROB2) have shown a significant decrease in respiratory rate post-induction using alfaxalone-HPCD as a dose-dependent phenomenon[10, 48]. Sigificant decrease in respiratory rate was shown to be caused by supraclinical doses of alfaxalone in a tolerance saftey study in dogs. [48] In summary, all studies recorded a certain degree of respiratory rate depression after anesthetic induction by clinical doses of alfaxalone-HPCD, propofol, etomidate and fentanyl/diazepam/propofol induction, although in some studies the respiratory depression was not shown to be statistically significant.

Weak evidence showed a very low incidence of post-induction apnea after both alfaxalone-HPCD and propofol induction. [10, 13, 21, 36] There was no significant difference in the incidence of post-induction apnea reported by the studies in this review. [10, 13, 21, 36] The occurrence of apnea was only reported by Ambros *et al* (2008). Both the alfaxalone-HPCD and propofol group had one apneic dog post-induction. [36]Apnea was not clearly defined in the study by Suarez *et al* (2012) (LOE1; ROB2) and Maney *et al* (2013) (LOE3 ; ROB1). Neither of the studies mentioned the length of time without respiratory movement was considered apnea.[13, 21] Therefore, the strength of evidence was downgraded from moderate to weak evidence. Apnea was defined as absence of respiratory movements for 30 seconds and one minute in the study conducted by Ambros *et al* (2008) (LOE3; ROB4) and Keates *et al* (2012) (LOE3; ROB3) respectively. [10]' [36] Studies that evaluated alfaxalone-HPCD without comparing it with other agents reported a low (0 – 4%) incidence of apnea when the agent was injected over 40 – 60 seconds at dose rates close to the recommended rate. [10, 38]'[24, 48]

In feline, patients (P), is alfaxalone-HPCD (I) versus other anesthetic agents (C) , a superior induction agent in terms of preservation of RR after induction (O)? Moderate evidence supports there being no significant difference in the post-induction respiratory rate after alfaxalone-HPCD and propofol induction. After alfaxalone-HPCD and propofol induction, the post-induction respiratory rate in cats reported by Mathis et al. (2012) (LOE1; ROB1) and Taboada (2010) (LOE 1; ROB2) was not significantly different (p=0.607 and 0.379 respectively). [16] Only two studies compared the post-induction respiratory rate of these two agents in cats, but neither of them assessed the significance of respiratory depression from baseline after induction.[12, 17] Studies that did not compare alfaxalone-HPCD induction with other agents reported a decrease in respiratory rate post-induction. [23, 25, 49] All studies included in this review reported a decrease in respiratory rate post-induction for both alfaxalone-HPCD and propofol.[12, 17, 23, 25, 49]

Weak evidence supports the conclusion that both alfaxalone-HPCD and propofol have a low to no incidence of apnea post-induction when used at the labeled dose rate. Taboada *et al* (2010) (LOE1; ROB2) was the only study that compared the incidence of post-induction apnea between alfaxalone-HPCD and propofol and reported no occurrence of apnea post induction after either induction protocol. Apnea was defined as absence of respiratory movements for one minute in this study.[12] Studies that did not compare alfaxalone-HPCD with other agents reported a low incidence (0-6%) of apnea. [25, 37, 49]

In canine patients (P), does alfaxalone –HPCD (I) versus other induction agents (C) , give a smoother and faster recovery (O)? Strong evidence showed that patients had smooth recoveries from anesthesia induced by either propofol or alfaxalone-HPCD until the animal was able to maintain sternal recumbency, with no statistical difference in recovery score between groups. There was no significant difference in the quality of early recovery graded by the simple descriptive scale (SDS) (p=0.086), visual analogue scale (VAS) (p=0.089) and recovery score in studies by Jimenez et al. (2012) (LOE1; ROB1) and Suarez et al. (2012) (LOE1; ROB2). Hunt et al. (LOE1;ROB2) also reported no difference in recovery quality between alfaxalone-HPCD and propofol induced dogs. This finding was consistent after maintenance with either inhaled sevoflurane or a constant rate infusion with the induction agent for anesthetic maintenance. [13, 15, 21, 36] There was insufficient evidence to determine the quality of recovery after the time

point at which dogs were able to maintain sternal recumbency. Suarez *et al* (2012) (LOE1; ROB2) reported that all dogs in the alfaxalone-HPCD group attempted to stand and walk with little or no difficulty (highest score), whereas one dog in the propofol group was reported to have some struggling during recovery.[13] There was no significant difference in recovery score between the two groups. [13] However, Jimenez *et al* (2012) (LOE1; ROB1) reported the propofol group had a significantly better late recovery (after animals were able to maintain sternal recumbency) than the alfaxalone-HPCD group under both simple descriptive scale (SDS) and visual analogue scale (VAS).[15] This study has been criticized, however, for failing to account for the pharmacokinetic elimination of the induction agents and the consequent potential for clearance of drug and effect.[50] There was also insufficient evidence to compare the time to extubation, head lift, sternal recumbency and standing between alfaxalone-HPCD and propofol. Suarez *et al* (2012) (LOE1; ROB2) and Keates *et al* (2012) (LOE3; ROB3) reported no significant difference in these time points between the agents.[10, 13]' However, Maney *et al* (2013) (LOE3 ; ROB1) reported significantly longer recovery and undesirable events in the alfaxalone-HPCD group.[21] Multiple factors may influence the quality and speed of recovery leading to differing results. As mentioned previously, the dose of alfaxalone-HPCD used this study (2.6 ± 0.4 mg kg^{-1}) exceeded the manufacturer's recommended induction dose of 2.0 mg kg^{-1} by 30%, which may have led to the undersirable events. Studies that have used the recommended clinical dose of alfaxalone-HPCD had smooth recoveries until the animal was able to maintain sternal recumbency. The difference in premedication used, length and type of procedure performed, maintenance anesthesia and gender of patient may all influence the quality of recovery. Therefore, care must be taken when comparing recoveries across studies.

There was insufficient evidence to compare the quality of recovery between fentanyl/diazepam/propofol and alfaxalone-HPCD induction. The average terminal half-life is 24 minutes for alfaxalone-HPCD, 91 minutes for propofol, 45 minutes for fentanyl and the half-life of diazepam is 3.2 hours [50-52]. Considering duration of anesthesia in alfaxalone-HPCD (96 - 360 minutes) and fentanyl/diazepam/propofol (80 – 355 minutes) groups, it is unlikely that alfaxalone-HPCD would have significant effect on the recovery.[50] The time to extubation was also not significantly different between two groups in this study. [11]

There was insufficient evidence to compare the quality of recovery between alfaxalone-HPCD and etomidate. Rodriguez *et al* (2012) (LOE3; ROB2) was the only study that compared these anesthetic agents. Recovery quality was reported to be better in dogs after anesthesia induced with alfaxalone-HPCD than etomidate. Time to standing and extubation, however, was longer in alfaxalone-HPCD induced dogs.[16]

Studies that evaluated the quality of recovery from anesthesia induced by alfaxalone-HPCD without comparing it with other agents described the recovery to be smooth and rapid (LOE1; ROB2), and had an overall recovery score of good to excellent.[14, 24, 48]

In feline patients (P), does alfaxalone-HPCD (I) versus other induction agents (C), give a smoother and faster recovery (O)? There was strong evidence that supports a recovery from anesthesia induced using alfaxalone-HPCD in cats without significant difference from administering propofol. [1, 12, 17] However, Mathis *et al* (2012) (LOE1; ROB1) reported that the number of patients paddling and trembling was significantly higher in the alfaxalone-HPCD group. Paddling and trembling were not included as one of the assessment criteria of the recovery quality in the study.[17] This has not been reported in previous studies and needs further investigation. Moderate strength of evidence showed that there were no beneficial analgesic properties from either alfaxalone-HPCD or propofol. Murison *et al* (2010) (LOE1; ROB1) assessed pain on recovery after ovariohysterectomy in propofol and alfaxalone-HPCD induced cats.[22] The recovery pain VAS of the propofol and alfaxalone-HPCD groups were not significantly different [22]. Since both alfaxalone-HPCD and propofol do not have analgesic properties, this may confound the anesthetic recovery scoring. With premedication, all studies that assessed alfaxalone-HPCD without comparing it to another agent reported a very good to excellent recovery. [23, 25, 37]

Limitations

This literature review has several limitations. Some studies might have been overlooked because the search was limited to studies that were published in English. Only those studies that were published in the peer-reviewed literature were included; exclusion of incompletely reported studies such as abstracts and conference proceedings or exclusion of studies completed but reported only in regulatory documents, or not reported at all, could introduce publication bias.

Conclusion

A total of 20 studies were included in this systematic review. Most studies compared the effects of alfaxalone-HPCD with that of propofol. In dogs, most studies showed that alfaxalone-HPCD provided smooth induction quality and good preservation of heart rate, without significant difference from propofol. The evidence behind the comparison of post-induction respiratory rate between alfaxalone-HPCD and propofol was contradictory and warrants further research. In cats, alfaxalone-HPCD has been shown to provide a smooth induction and recovery without significant difference from propofol. The post-induction respiratory effects of alfaxalone-HPCD in cats were not significantly different from that of propofol. More research is required to compare the cardiovascular effects of alfaxalone-HPCD induction with other agents in cats. Strong evidence showed dogs and cats have smooth recoveries after induction using either alfaxalone-HPCD or propofol, before reaching sternal recumbency.

Footnotes

a: Alfaxan®, Jurox Pty Ltd, Rutherford, NSW, Australia

b: Propofol Vet®, Abbott Animal Health, UK

c: PropoClear®, Pifzer Animal Health, UK

Figure Legends

Figure 1. Flow diagram showing pathway for literature search for alfaxalone-HPCD and for manuscript selection

Figure 2. The Level of Evidence (LOE) and risk of bias grading (ROB) assigned to the included studies of the use of alfaxalone-HPCD in dogs (n=14).

Figure 3. The Level of Evidence (LOE) and risk of bias grading (ROB) assigned to the included studies of the use of alfaxalone-HPCD in cats (n=9).

Table Legends

Table 1. List of included studies in this systematic review

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Table 1

Author	**Year**	**Type of Study**	**Risks of Bias**	**Rating**	**Species (Number)**	**Approved dose rate**
Ambros B et al.[36]	2008	Prospective two period cross-over experimental study	Selection bias - No random allocation Detection bias - No blinding in outcome assessors - May affect scoring Other - Conflict of interest - Funded by Jurox Pty Ltd.,	LOE3 ; ROB4	Dogs (n=6)	Yes

			which developed Alfaxan			
Amengual M et al.[20]	2013	Prospective randomized blinded clinical study		LOE1; ROB1	Dogs (n=60)	Yes
Bortolami E et al. [47]	2013	Prospective randomized blinded clinical controlled trial	Other - Conflict of interest - Funded by Eurovet Animal Health	LOE1; ROB2	Cats (n=45)	Yes
Herbert GL et al. [14]	2013	Prospective randomized clinical trial	Detection bias - No blinding - May affect scoring	LOE1; ROB2	Dogs (n=38)	Yes
Hunt JR et al. [1]	2013	Prospective, randomized, blinded clinical study	Other - Difference in induction dose	LOE1; ROB2	Dogs (n=40); Cats (n=48)	Yes
Jimenez CP et al.[15]	2012	Prospective randomized clinical trial		LOE1; ROB1	Dogs (n=42)	Yes

Keates H et al. [9]	2012	Prospective randomized , crossover experimental study	Conflict of interest - Author was an employee of Jurox Pty Ltd.	LOE3; ROB2	Dogs (n=6)	Dosed at 1x, 2x, 5x, 10x, and 20x of labelled doses
Maddern K et al. [38]	2010	Prospective randomized blinded clinical trial		LOE1; ROB1	Dogs (n=85)	Yes
Mathis A et al. [17]	2012	Prospective, blinded, randomized clinical trial		LOE1; ROB1	Cats (n=93)	Yes
Maney JK et al. [21]	2013	Prospective, randomized blinded crossover, experimental study		LOE3; ROB1	Dogs (n=8)	Dosed at 2x labelled dose
Michou JN et al. [18]	2012	Prospective, blinded, randomized crossover clinical trial		LOE1; ROB1	Dogs (n=30)	Yes
Muir W et al. [48]	2008	Prospective randomized blinded four-way crossover experimental study	Other - Conflict of interest - Funded by Jurox Pty Ltd., which developed	LOE3; ROB2	Dogs (n=8)	Dosed at clinical (labelled) and supraclinical (off labelled)

			Alfaxan			doses
Muir W et al. [23]	2009	Prospective randomized blinded four-way crossover experimental study	Other - Conflict of interest - Funded by Jurox Pty Ltd., which developed Alfaxan	LOE3; ROB2	Cats (n=8)	Dosed at clinical (labelled) and supraclinical (off labelled) doses
Murison PJ et al. [21]	2010	Prospective blinded randomized clinical trial	-	LOE1; ROB1	Cats (n=35)	Yes
O'Hagan BJ et al. [24]	2012	Prospective clinical trial	Detection bias - No blinding in outcome assessors - May affect scoring Other - Conflict of interest - Funded by	LOE5 ; ROB3	Cats (n=34)	Yes

			Jurox Pty Ltd., which developed Alfaxan			
O'Hagan BJ et al.[23]	2012	Prospective clinical trial	Detection bias - No blinding in outcome assessors - May affect scoring Other - Conflict of interest - Funded by Jurox Pty Ltd., which developed Alfaxan	LOE5 ; ROB3	Dogs (n=25)	Yes
Psatha E et al. [10]	2011	Prospective randomized clinical trial	Attrition bias - Missing data	LOE1; ROB2	Dogs (n=40)	Yes
Rodriguez JM et al.	2012	Randomized , blinded cross-over study	Selection bias	LOE3; ROB2	Dogs	Dosed at 2x

[15]			- Only beagles were used in this study		(n=8)	labelled dose
Suarez MA et al.[12]	2012	Prospective randomized clinical trial	Detection bias - No blinding in outcome assessors - May affect scoring	LOE1; ROB2	Dogs (n=14)	Yes
Taboada FM et al. [11]	2010	Prospective randomized clinical trial	Detection bias - No blinding in outcome assessors - May affect scoring	LOE1; ROB2	Cats (n=39)	Yes
Whittem T et al. [40]	2008	Prospective randomized two period cross-over experimental study	Other - Conflict of interest - Funded by Jurox Pty Ltd., which	LOE3; ROB2	Cats (n=6)	Dosed at clinical (labelled) and supraclinical (off

			developed Alfaxan			labelled) doses
Zaki S et al. [36]	2009	Prospective clinical trial	Selection bias - No random allocation Detection bias - No blinding in outcome assessors - May affect scoring	LOE2; ROB3	Cats (n=35)	

Figure 1.

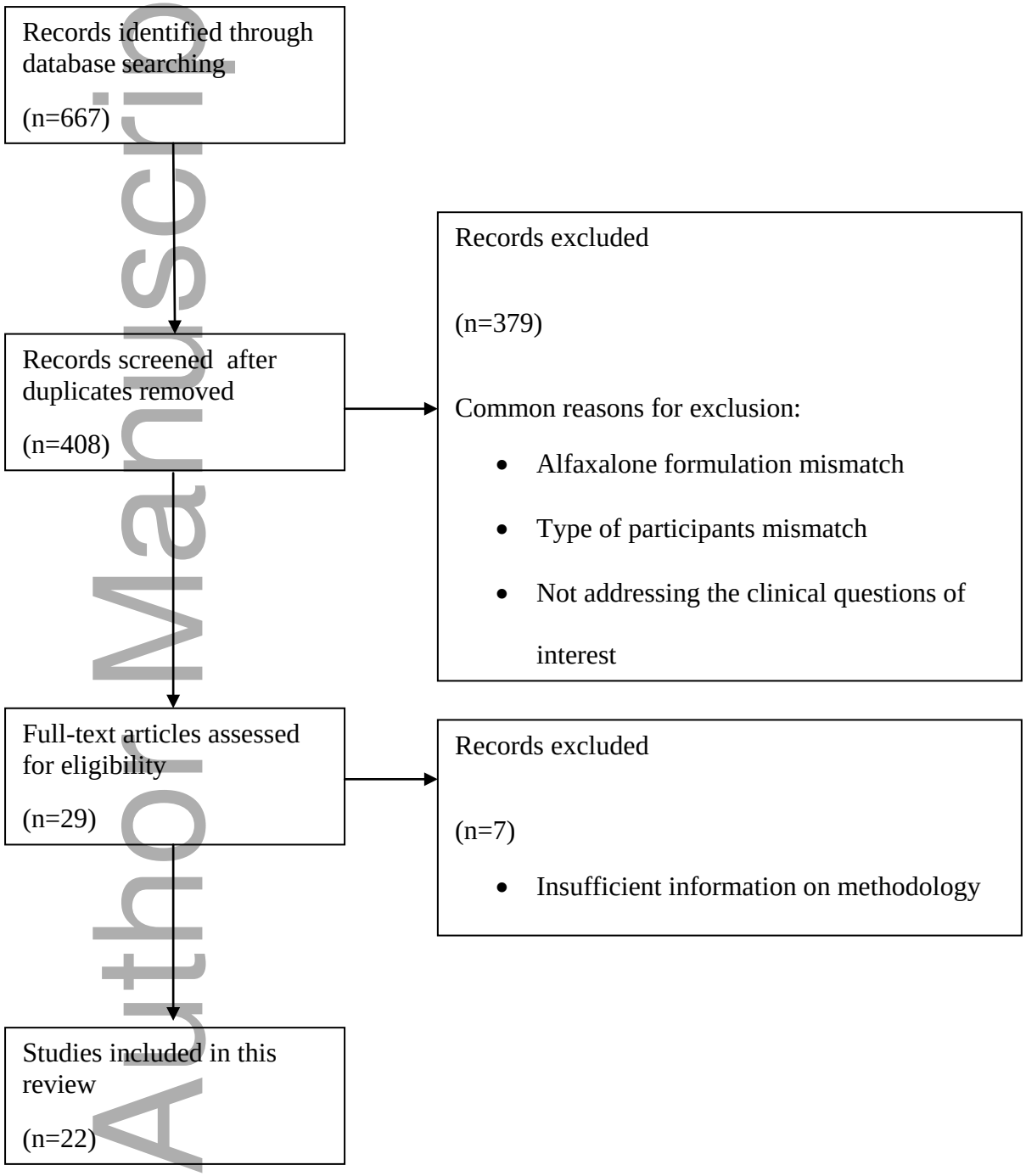
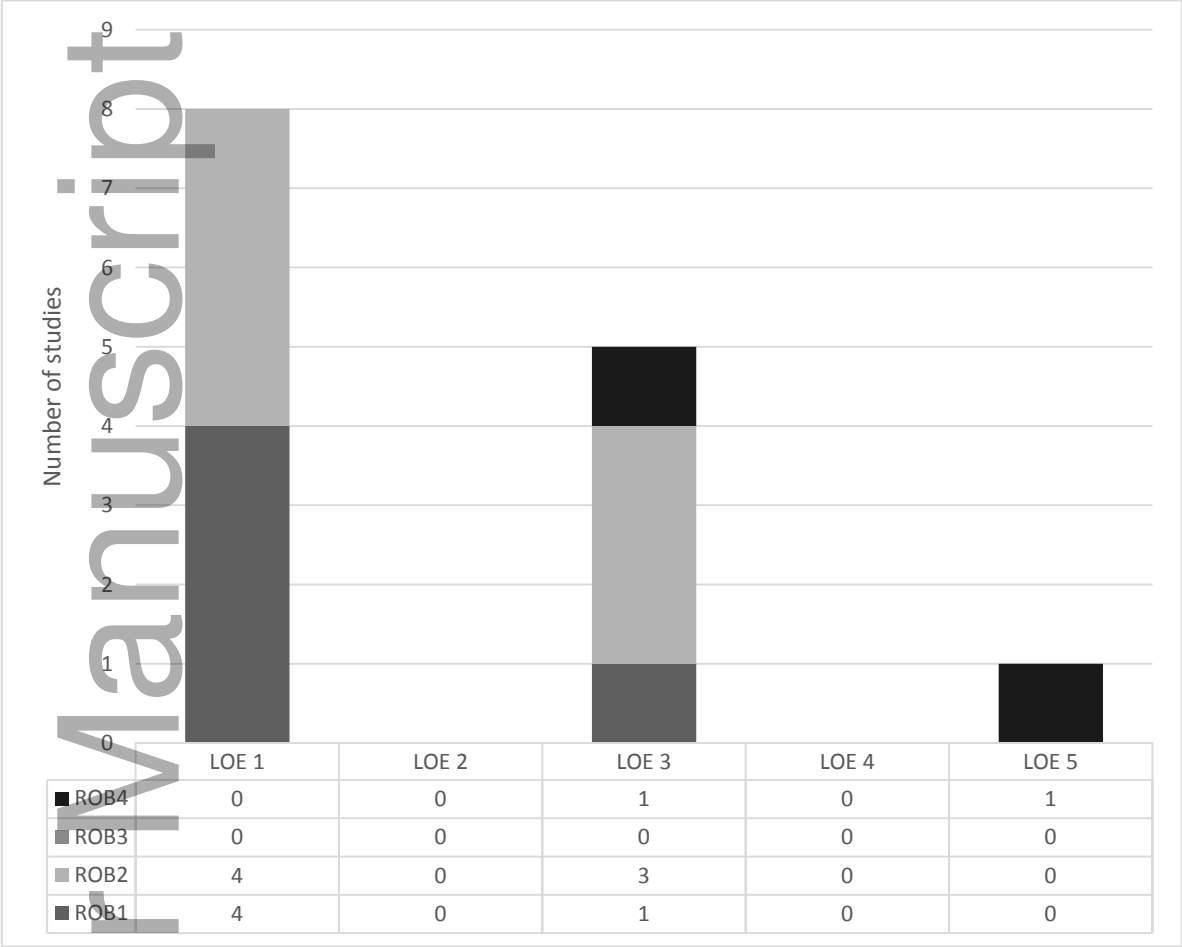
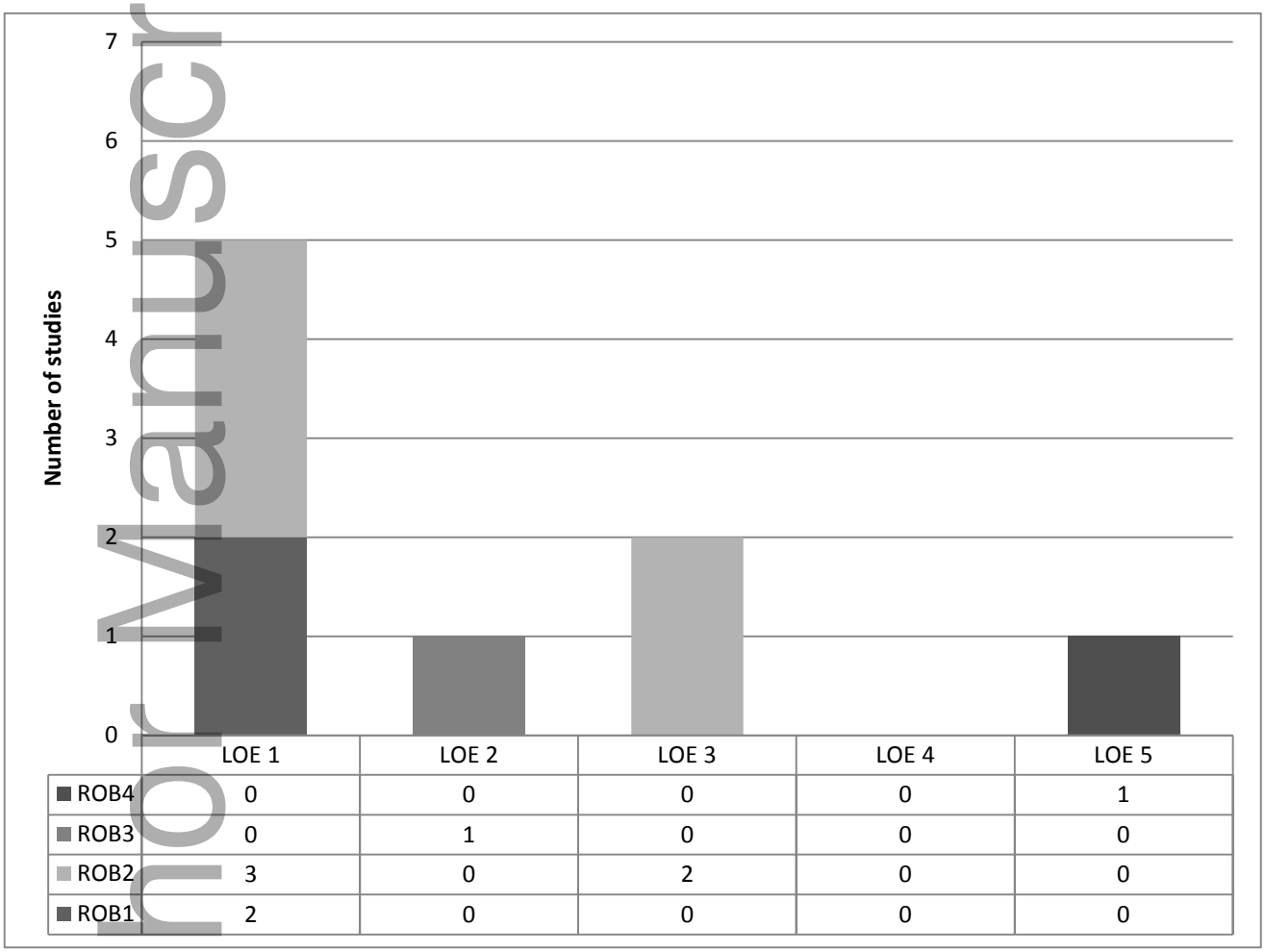


Figure 2



	LOE 1	LOE 2	LOE 3	LOE 4	LOE 5
ROB4	0	0	1	0	1
ROB3	0	0	0	0	0
ROB2	4	0	3	0	0
ROB1	4	0	1	0	0

Figure 3.



	LOE 1	LOE 2	LOE 3	LOE 4	LOE 5
ROB4	0	0	0	0	1
ROB3	0	1	0	0	0
ROB2	3	0	2	0	0
ROB1	2	0	0	0	0

Author/s:
Chiu, KW;Robson, S;Devi, JL;Woodward, A;Whittem, T

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