Intravenous lignocaine for perioperative analgesia – a systematic review identifying current applications and future potential.

Research Report

For MMed (Anaesthesiology)

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Contents:

Intravenous lignocaine for perioperative analgesia – a systematic review identifying current applications and future potential.

Dr. JG Vorster – Primary Investigator
Prof. BJS Diedericks – Supervisor
Department of Anaesthesiology, University of the Free State

28 August 2018

Dear Reviewer,

Thank you for the opportunity to present this research manuscript for your consideration. This manuscript illustrates the scientific foundation of this review and the systems that were used for the collection of literature, extraction of information and ultimately the synthesis of a report.

To clarify the context of this review it must be stressed that the post-graduate rule book of the University of the Free State states that a limited review be submitted in fulfillment of the requirement to complete a MMed degree. Therefore the search was limited to one database over a 10-year period. A more comprehensive manuscript may be considered for submission to the Southern African Journal of Anaesthesia and Analgesia (SAJAA) for publication.

This qualitative review was chosen to broaden the potential scope of literature that was included in the review. The report outlines the methods used as well as the results and conclusions obtained. This review has been registered on the PROSPERO database of systematic reviews and has been approved by the Health Sciences Research Ethics Committee of the Faculty of Health Sciences – University of the Free State as well as the Free State Department of Health (confirmation letters included with this manuscript).

We trust that this manuscript will prove both interesting to our field as well as offer recommendations that are applicable in our daily clinical practice. We hope to illuminate some of the uncertainty surrounding the practice of IV lignocaine for perioperative pain, clearly identify which patients may benefit from its use in our setting and transform paucity in the literature into recommendations for future clinical research.

Thank you for your time in reviewing our manuscript.

Kind regards,

Dr. Johannes Vorster
Registrar – Department of Anaesthesiology
Universitas Academic Complex

Declaration of work:

I, Dr Johannes Gysbertus Vorster, submit this manuscript in support of my MMed (Anaesthesiology) degree. I declare that the work contained herein is my own original work and no part of the text has been reproduced verbatim from another text. The source material used to conduct this research and compile this manuscript is referenced under the appropriate section.

The illustrations used in this manuscript, which are from other material, are referenced to credit the source. All other tables, illustrations and devices are of my own work.

This manuscript was overseen by my study leader and corrections made by myself.

Signed:

Dr. JG Vorster at Bloemfontein on 20 November 2018

Dedication:

This work is dedicated to my study leader, Prof. BJS Diedericks, for always inspiring his registrars to question the science of anaesthesiology and better the field through the contribution of knowledge.

I further dedicate this work to my earliest mentor in my career, Dr. J Espinaco Valdés, who taught me the value of good research and making it good clinical practice.

Abbreviations

The following abbreviations are used in this text:

CABG – Coronary Artery Bypass Grafting

CEA – Continuous Epidural Analgesia

ERAS – Enhanced Recovery After Surgery

GIT – Gastro Intestinal Tract

IV – Intravenous

IVI – Intravenous Infusion

NSAIDs – Non-steroidal Anti-inflammatory Drugs

PACU – Post Anaesthetic Care Unit

PCEA – Patient Controlled Epidural Analgesia

POD – Post-operative Day

PONV – Post-op Nausea and Vomiting

PRISMA – Preferred Reporting In Systematic Reviews and Meta-Analysis

RCT – Randomized Control Trial

mcg – Microgram

mg – Milligram

mg/kg – Milligram per kilogram

mg/kg/hr – Milligram per kilogram per hour

mg/min – Milligram per minute

List of tables and illustrations

The following tables and illustrations are featured in this manuscript:

Chapter 1:

Research protocol

Intravenous lignocaine for perioperative analgesia – a systematic review identifying current applications and future potential.

Dr. JG Vorster – Primary Investigator
Prof. BJS Diedericks – Supervisor
Department of Anaesthesiology, University of the Free State

RESEARCH PROTOCOL

Version 4 – Post Revision by Supervisor – Dated: 22 October 2017

Introduction:

Lignocaine as an intravenous (IV) adjunct has drawn attention over the past decade. A 2011 meta-analysis from Vigneault et al concluded several advantages to IV lignocaine, such as reducing pain at rest, cough and movement whilst reducing opioid requirements, but questioned the safety profile regarding toxicity.[1] Subsequently a 2015 Cochrane review by Kranke et al. found limited evidence of increased adverse events such as death, arrhythmias or lignocaine toxicity but questioned the role of IV lignocaine infusion versus established continuous analgesic interventions such as epidural infusions.[2] They reported moderate to low evidence for this intervention – citing statistical heterogeneity and small study sizes. Conversely a 2016 article by Eipe and colleagues intravenous lignocaine has been reported to offer proven efficacy when used as a peri-operative analgesic compared to epidural analgesia, in certain surgical groups, further suggesting a practical protocol for the safe administration thereof.[3]

In the current era of peri-operative analgesia, opioid-sparing strategies using multi-modal approaches is evidence based and regimes reducing opioids are proven to cause fewer adverse effects such as nausea and ileus, leading to enhanced recovery. [4]

Despite literature supporting the use of IV lignocaine in multi modal analgesia, this intervention is not widely used due to lack of clarity on the subject. [3]

Aim:

According to the PICO principle [5] as applied to systematic reviews, the research question is formulated and tested as follows:

Population:	Patients undergoing anaesthesia for surgery.
Intervention:	I.V. lignocaine infusion for peri-operative analgesia.
Comparison:	Conventional modalities of analgesia, e.g.: opioid analgesia.
Outcome:	Reduced requirement of conventional analgesics and their adverse effects.

Therefore our research question is: In patients undergoing anaesthesia for surgery, does I.V. lignocaine infusions for peri-operative analgesia, compared to conventional modalities of analgesia, decrease those analgesic requirements and adverse effects?

To answer this question we will examine past as well as recent literature and perform a primarily qualitative review clarifying the application of this intervention with relevant quantitative references in terms of safe dosing protocols. Unique to our study will be the categorization of the evidence according to the surgical disciplines available at Universitas Academic Hospital.

Thus the question will explore the following avenues:

- General advantages and/or disadvantages to peri-operative I.V. lignocaine as an analgesic modality as well as safe dosing protocols.
- To guide the application of the findings we will aim to provide discipline specific recommendations to motivate for, or advise against, the use of I.V. lignocaine in the perioperative period.
- A resultant outcome from this method will be identification of paucity in the current literature and offer a direction to which discipline's surgical populations may be investigated by future clinical trials.

Methodology

Study design:
This study will be a qualitative systematic review.

Registration on a Systematic Review database:
The study will be registered with the PROSPERO database, which is an international prospective registry for systematic reviews and a subsidiary of the National Institute for Health Research in the UK.

Data handling:
All relevant data will be stored electronically and a backup copy uploaded to a Drop Box folder, which is accessible by the primary investigator and the supervisor.

Hard copies made of resource documents and articles involved in the review will be stored in a file kept at the primary investigators' home office. This file will be immediately available to the supervisor if requested.

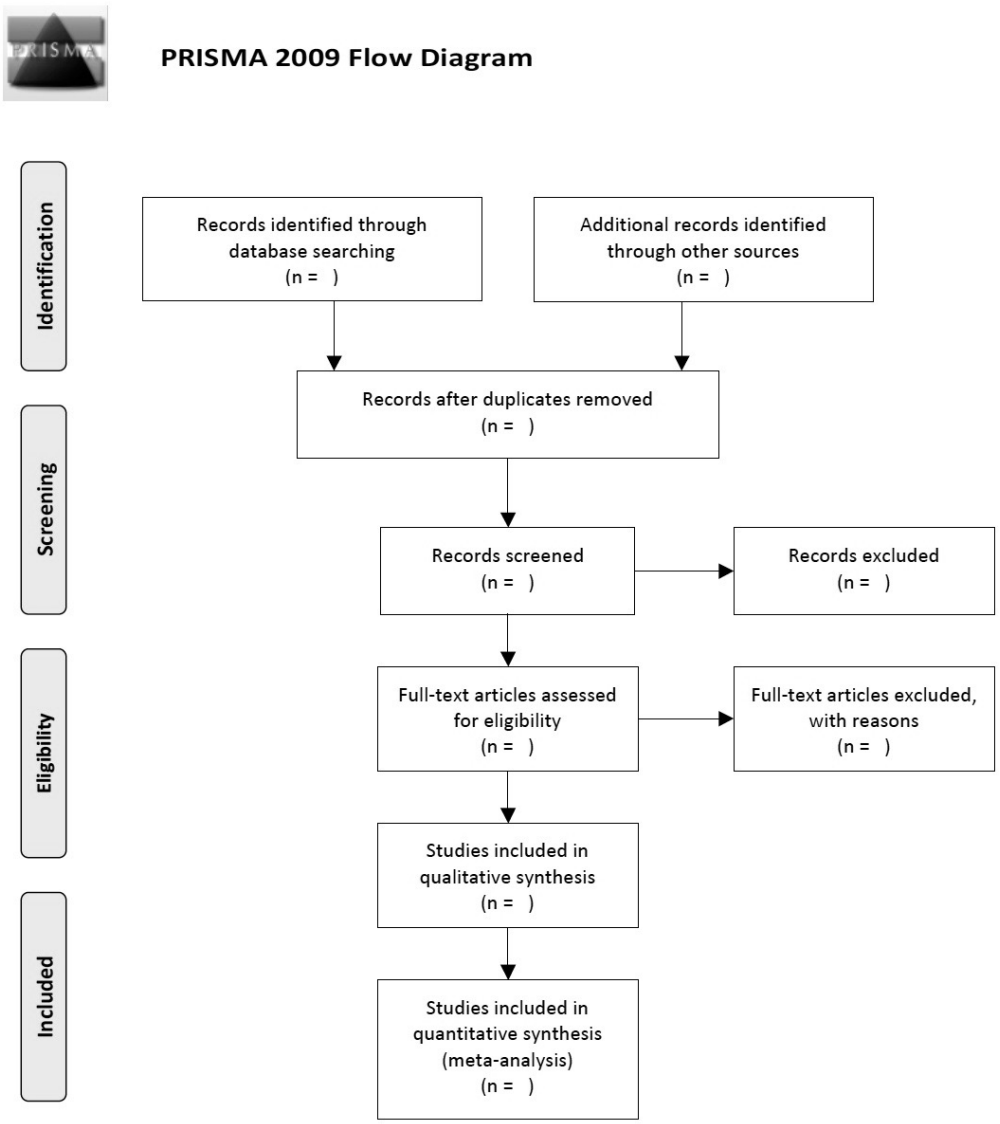
Information source:
The PubMed database using the advanced search tool available on the PubMed website: https://www.ncbi.nlm.nih.gov/pubmed/advanced will be used to identify potential articles for review. This database offers more than 28 million citations and includes the well known MEDLINE database.

Search Strategy:
The following search terms will be used in the initial search:

- Lignocaine
- Intravenous
- Perioperative
- Analgesia

Selection process of articles identified in the initial search:
The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) offers a comprehensive guide for performing a systematic review. [6]

The following flow diagram from the PRISMA statement will be used to filter the articles identified in the initial search to the articles that will be included in the review **(Diagram 1)**:



Screening criteria:

- Articles from the past 10 years.
- Articles from human observations.
- Articles written in English.
- Full text articles.

Eligibility criteria:

- Meta analysis.
- Systematic reviews.
- Randomized controlled trials.
- Cohort studies.
- Case control studies.
- Case series or single case reports.
- Published protocols.
- *Meets inclusion criteria and none of the exclusion criteria.*

Inclusion criteria:

- Studies in keeping with the PICO formulated question for this review:
  - Mention of peri-operative anaesthesia
  - Mention of intravenous lignocaine
  - Mention of effect on conventional analgesic modalities

- Studies reporting on surgical populations comparable to those at our institution – this is to ensure that the findings are applicable to our setting.
  Therefore:
  - Neurosurgery
  - Plastic surgery
  - Orthopaedic surgery including athroplasty
  - Vascular surgery
  - Gastrointestinal surgery
  - Hepatobiliary surgery
  - Mamma and endocrine surgery
  - Paediatric surgery
  - Thoracic surgery
  - Cardiac surgery
  - Urology
  - Ear, Nose and Throat surgery
  - Obstetric and gynecological surgery

Exclusion criteria:

- Unpublished articles ("grey" research)
- Clinical research not citing ethical oversight and approval of interventions.

Data collection process:
Articles included for the review will be read and the information relevant to the question and outcomes of this review will be highlighted and flagged for ease of recalling the data and transferring it to a collection device. Each article will be **numbered** sequentially giving each article an **article number** for tracking.

The data collection device will be an electronic table (Microsoft Excel sheet) where all the relevant findings will be typed in by the investigator. The internal article number will be entered adjacently. On a separate sheet, in the same file, the reference list of articles will be kept with the internal article numbers and the corresponding article's full reference.

The data collection table will be divided into the following headings to group and sub-group data:

Outcome 1: General findings and safety
- Advantages mentioned.
- Disadvantages mentioned.
- Safety mentioned.
- Dosing protocol mentioned.

Outcome 2: Application in specific disciplines mentioned
(Headings for each surgical discipline mentioned in the inclusion criteria).

Outcome 3: Disciplines not mentioned or intentionally excluded with reasons for exclusion.

An example of the data collection table is attached as **Appendix A.**

An example of the reference list is attached as **Appendix B.**

Detection of bias in included articles:
The Cochrane risk of bias tool will be used when reading included articles to identify possible bias.[7]
If potential bias is identified the possibility of bias will be included in the information transferred to the data collection table to promote transparency of the limitations that may be inborn to some findings.

A copy of the Cochrane risk of bias tool is included as **Appendix C.**

Analysis:

Consultation with Prof. G Joubert, Department of Biostatistics, concluded that specific analysis by a biostatistician is not required prior to compiling a report on the data collected.

Methods to be used for the compilation of the research report:

Writing of the research report will follow the PRISMA checklist for writing a systematic review. [6] The checklist details the headings as well as the content that should be included under each heading. This format may be used for more extensive reviews such as a meta-analysis and therefore the headings not applicable to this research report will be omitted during compilation.
A copy of the PRISMA checklist is attached as **Appendix D**.

Synthesis of data during the writing of the report:

Data synthesis will follow the format of the data collection table to keep the format and presentation of the findings in line with the research question.
The data will therefore be presented in the three groups of outcomes under the heading of "Summary of Evidence" in the report.

Below is an example of a completed data collection form **(Figure 1)**:

Data collection table - Lignocaine systematic review:				
Outcome 1: General findings and safety				
1.1. Advantages of lignocaine IV mentioned:				**Article number:**
Lignocaine reduces peri-op morphine use. Early food tollerance.				Article 1
Lignocaine reduced morphine use. Less ileus post op.				Article 7
1.2. Disadvantages of lignocaine IV mentioned:				**Article number:**
Lignocaine may cause sedation.				Article 2
1.3. Safety mentioned:				**Article number:**
Safe if dose kept less than 2mg.kg.hr				Article 3
1.4. Dosing protocols mentioned:				**Article number:**
IV infusion started with a bolus at induction of anaesthesia and continued post op.				Article 4
Outcome 2: Specific disciplines mentioned				
2.1. Neuro surgery mentioned:				**Article number:**
Not effective in craniotomy analgesia				Article 8
2.2. Plastic surgery mentioned:				**Article number:**
None - refererred to section 3				N/A
2.3. Orthopaedics mentioned:				**Article number:**
May be effective in hip athroplasty, but only in combination with opioids.				Article 12
Outcome 3: Disciplines not mentioned or specified as not investigated				
	Not mentioned			
	Yes		**Mentioned but exluded:**	**Article number:**
			Reason?	
3.1. Cardiac surgery	X			
3.2. Plastic surgery	X			
3.3. Paediatric surgery		X	Exlcusion criteria - patients <18 y/o	Articles 2,5,7
3.4. Neurosurgery	N/A	N/A		

Data Collection Table | Reference list | +

Example showing how statements will be drawn from the data collection sheet:

- Single statement with a single reference:
  "I.V. Lignocaine is safe if the dose is maintained below 2mg.kg.hr.[1]"

- Single statement with multiple references:
  "I.V. lignocaine reduces morphine requirements.[2,3]"

- Multiple statements from a single reference:
  "Lignocaine may cause increased sedation levels. [4]"
  "Several articles did not include paediatric patients due to the inclusion criteria selecting patients older than 18. [4,5,6]"

Statements drawn from the data collection sheet will of course follow a logical sequence and not be written in short hand as in the data collection sheet. The end result should be a publishable manuscript presenting the collected data in an easily readable, logical and flowing style rather than just a list of random facts.

Referencing of articles:

Note in the example that the reference numbers in the report would not necessarily be the same as the article number. This is because the *article numbers* will follow the sequence that articles are read where as *referencing in the report will follow the sequence in which statements are drawn* from the data collection form.

Once a statement is made in the report the next *number in the sequence of references* will be added in superscript then the *article number* will be used to immediately find the reference on the reference list sheet. The Vancouver format reference will then be transferred to the references at the end of the report and allocated to the number corresponding to the superscripted number of the statement in the text.

Implementation of findings:

The research report will be presented to the Department of Anaesthesiology at Universitas Academic Hospital should the findings prove significant. This may encourage colleagues to use this intervention and guide safe practice protocols and appropriate patient selection.

Additionally future clinical trials may be undertaken based on the need identified from this review.

Following conclusion of the study and compilation of the report, the manuscript may also be submitted for publication at the discretion of the primary investigator and the supervisor.

Time schedule:

October 2017:	Writing and review of protocol.
November 2017:	Submission of protocol to Health Sciences Research Ethics Committee.
January – February 2018:	Primary investigator in preparation for FCA part II exams. (Research activities suspended).
March 2018:	Research resumes with data base search and collection of articles that may be included in the study. Articles will be printed and numbered.

April – June 2018:	Articles are read and relevant data entered on the data collection sheet.
July 2018:	Compilation of research report.
August 2018:	Departmental presentation of report. Consideration for publication and submission of manuscript.

Budget:

The resources mentioned in this protocol are available at **no cost** and include:

- PRISMA documents
- PROSPERO registration
- Cochrane bias identification tool
- PubMed advanced search
- Free Full Text articles

Articles that require an access fee may be prohibitively expensive to obtain.
Access to such articles will be sought via the University of the Free State library service using the institutional subscription for that journal.

Printing costs will be minimal as most of the study is conducted electronically – communication will be by email, records kept electronically etc.
The articles will however be printed at the primary investigator's home office at his expense and is estimated to be less than R200 in total.

Including miscellaneous stationary items such as ring binders etc. **the total cost of the study should not exceed R500.**

Ethical aspects:

The protocol will be submitted to the Health Sciences Research Ethics Committee of the University of the Free State for review and approval prior to conducting the research.

This review does not involve collection of data from individual participants and therefore informed consent is not applicable for data collection.

This is not a clinical trial and therefore can cause no harm to any participants.

Bearing in mind though that the findings of the report may influence clinical practice the articles reviewed must be ethically sound and articles mentioning clinical research must make specific mention of ethics approval.
Articles identified for inclusion in the study not adhering to this will be excluded and mentioned as identified but excluded due to lack of ethical context.

Resources used for writing this protocol:

- PRISMA-P 2015 checklist recommended items to address in a systematic review protocol. [8]
- Department of Biostatistics manual for beginner researchers. [9]
- From idea to research - DVD presentation by Prof. B Biccard[10]

References for protocol:

1. Vigneault, L., Turgeon, A.F., Côté, D. et al. Postoperative pain control. Can J Anesth/J Can Anesth. 2011; 58(1):22-37.

2. Kranke P, Jokinen J, Pace N, Schnabel A, Hollmann MW, Hahnenkamp K, Eberhart LHJ, Poepping DM, Weibel S. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD009642. DOI: 10.1002/14651858.CD009642.pub

3. Eipe N, Gupta S, Penning J. Intravenous lidocaine for acute pain: an evidence-based clinical update. [Internet]. BJA Education. 2016 [accessed 5 October 2017, cited 14 October 2017]. Available from: http://bjaed.oxfordjournals.org/content/bjaed/early/2016/04/11/bjaed.mkw008.full.pdf

4. Garimella V, Cellini C. Postoperative pain control. Clin Colon Rectal Surg. 2013;26(3):191-196.

5. Subject Guides: Systematic Reviews: Using PICO or PICo [Internet]. Libguides.murdoch.edu.au. 2017 [accessed 5 October 2017, cited 14 October 2017]. Available from: http://libguides.murdoch.edu.au/systematic/PICO

6. BMJ (OPEN ACCESS) Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. BMJ 2009;339:b2535, doi: 10.1136/bmj.b253

7. Assessing Risk of Bias in Included Studies | Cochrane Bias [Internet]. Methods.cochrane.org. 2017 [accessed 8 October 2017, cited 14 October 2017]. Available from: http://methods.cochrane.org/bias/assessing-risk-bias-included-studies

8. Shamseer L, Moher D, Clarke M, et al. PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647

9. Joubert G, Bam R, Cronjé H. How to write a protocol - A manual for beginner researchers. Bloemfontein: Department of Biostatistics - University of the Free State; 2008.

10. Biccard B. From idea to research. Bloemfontein: Department of Anaesthesiology - University of the Free State; 2014. [DVD media]

Chapter 2:

Article Manuscript

Intravenous lignocaine for perioperative analgesia – a systematic review identifying current applications and future potential.

Dr. JG Vorster – Primary Investigator
Prof. BJS Diedericks – Supervisor

Department of Anaesthesiology, University of the Free State

Abstract

Background: Opioid-sparing analgesia has become the standard of care for perioperative analgesia. Lignocaine as an IV infusion is an attractive option for inclusion in such regimes due to its ease of administration compared to neuraxial/block techniques. It has an acceptable safety profile when used correctly.

Methods: The PRISMA statement for writing systematic reviews was followed in writing this review. Due to time and financial limitation, the search was limited to the PubMed database. A yield of 14 articles was included for review. Article results were tabulated and a score given for the level of strength for each article and a qualitative appraisal done of each article. This manuscript highlights the important findings.

Results: There is a large body of evidence to support the use of this intervention for perioperative analgesia in *predominantly* abdominal surgery. Optimal results are achieved if it is used as an adjunct rather than a sole analgesic. There exists large paucity in the literature regarding its use in all surgical disciplines.

Conclusion: IVI lignocaine should be considered in any opioid-sparing multi modal perioperative analgesic regime - along with paracetamol, NSAIDs and gabapentanoids - in select surgical groups. It is specifically useful as a rescue analgesic when other conventional modalities are contraindicated or failed. Further high quality prospective trials are needed in the surgical disciplines lacking literature to support or refute its use.

Key words: *lignocaine; intravenous; perioperative; analgesia*
Ethics approval number: **UFS-HSD2017-1451**
PROSPERO registration number: **CRD42018092387**

Introduction

Rationale for the review:

In the current era of peri-operative analgesia, opioid-sparing strategies using multi-modal approaches is evidence based and regimes reducing opioids are proven to cause fewer adverse effects such as nausea and ileus, leading to enhanced recovery.[1] Lignocaine as an intravenous (IV) adjunct has drawn attention over the past decade. A 2011 meta-analysis from Vigneault et al concluded several advantages to IV lignocaine, such as reducing pain at rest, cough and movement whilst reducing opioid requirements, but questioned the safety profile regarding toxicity.[2] Subsequently a 2015 Cochrane review by Kranke et al. found limited evidence of increased adverse events such as death, arrhythmias or lignocaine toxicity but questioned the role of IV lignocaine infusion versus established continuous analgesic interventions such as epidural infusions. They reported moderate to low evidence for this intervention – citing statistical heterogeneity and small study sizes.[3] Conversely in a 2016 article Eipe and colleagues reported proven efficacy of intravenous lignocaine, from a clinical audit of their acute pain service, when it was used as rescue analgesia in certain surgical groups - further suggesting a practical protocol for the safe administration thereof.[4]

Despite literature supporting the use of IV lignocaine in multi modal analgesia, this intervention is not widely utilized due to lack of clarity on the subject. [4] This review was conducted to illuminate some of the uncertainty surrounding this practice and specifically clarify the application of this intervention as well as identify paucity in the literature where future research may be endeavored.

Objectives:

According to the PICO principle[5] as applied to systematic reviews, the research question was formulated as follows:

Population:	Patients undergoing anaesthesia for surgery.
Intervention:	I.V. lignocaine infusion for peri-operative analgesia.
Comparison:	Conventional modalities of analgesia, e.g.: opioid analgesia.
Outcome:	Reduced requirement of conventional analgesics and their adverse effects.

Therefore our research question was: **In patients undergoing anaesthesia for surgery, does I.V. lignocaine infusions for peri-operative analgesia, compared to conventional modalities of analgesia, decrease those conventional analgesic requirements and adverse effects?**

The question was explored under the general advantages and/or disadvantages to peri-operative I.V. lignocaine, discipline specific use of the modality and identification of areas lacking information in the current literature to offer a direction in which surgical disciplines' future trials of lignocaine, as an analgesic adjuvant, should be done.

Methods

Protocol and registration:

A comprehensive protocol was written by the researcher and reviewed and approved by the study leader. It was subsequently submitted and approved by the Health Sciences Research Ethics Committee of the University of the Free State - Faculty of Health Sciences, **Approval number: UFS-HSD2017-1451 (Letter of approval: Appendix E)**, as well as the Free State Department of Health **(Letter of approval: Appendix F).**

Following approval by the institutional ethics committee and regional governing body, the review was registered and approved for publication in the PROSPERO database of reviews. **(Registration number: CRD42018092387)**

Search criteria:

Screening criteria included full text articles in English, from the past 10 years, on human research.

Eligibility ranged from meta-analysis to case reports and protocols, provided that the text was published and subsequently met the inclusion criteria and none of the exclusion criteria.

Inclusion criteria:

- Studies in keeping with the PICO formulated question for this review: Mention of **peri-operative anaesthesia** using **intravenous lignocaine** and the **effect on conventional analgesic modalities (or placebo).**
- Studies reporting on surgical populations comparable to those of a tertiary institution – this is to ensure that the findings are broadly applicable.

Exclusion criteria:

- Unpublished literature ("grey" research)
- Clinical research not citing ethical oversight and approval of interventions.

Information Sources:

The PubMed database using the advanced search tool available on the PubMed website: https://www.ncbi.nlm.nih.gov/pubmed/advanced was used to identify potential articles for review.

Search and selection:

The search terms that were used in the initial search was: "**Lignocaine"**; "**intravenous"**; "**perioperative"** and "**analgesia".**

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement offers a comprehensive guide for performing a systematic review and its flow diagram was used to select the relevant studies from the search results, and this application is illustrated in **Diagram 2** under results. [6]

Data collection process:

Articles included for the review were read in the **PP-ICONS approach**.[7] Thereafter the information relevant to the question and outcomes of this review was transferred to a data collection device in that format. Each article was **numbered** sequentially giving each article an **article number** for tracking.

The data collection device was an **electronic table on an Excel sheet** (Microsoft Office 2011 for Mac – Microsoft Corporation, Washington USA). The investigator typed all the relevant results as summary findings on this sheet. The internal article number was entered adjacently. On a separate sheet, in the same file, the reference list of articles was kept with the internal article numbers and the corresponding article's reference.

The data in the collection table was divided into: **Outcome 1** - General findings and safety, **Outcome 2 -** application in specific disciplines and **Outcome 3 -** disciplines not mentioned or intentionally excluded with reasons for exclusion (to identify directions for future research).

Risk of bias in individual studies:

The Cochrane risk of bias tool was used when reading included articles to identify any major bias.[8] If potential bias was identified the possibility of bias was included in the information transferred to the data collection table to promote transparency of the limitations that may be inborn to some findings.

Synthesis of results:

The findings are presented in a table with the article name and the findings relevant to the question of this review. It is characterized in this way for ease of reading when interpreting the results and to present it in the format in keeping with that of the articles reviewed, to create a degree of uniformity in the literature.

Each article is weighted by its **strength of evidence** and is given as a Level 1-5, which is used in literature locally and internationally, to indicate the experimental validity of the results. *(Table included with results section for convenience of reading – see table 1).*

In the summary of evidence section in the discussion, statements were synthesized from this table as well as the data collection sheet and presented in the order of the specified outcomes for simplicity and continuity.

Furthermore, to ensure methodological accuracy, this report was compiled in compliance with the format set forth by the PRISMA statement. [6]

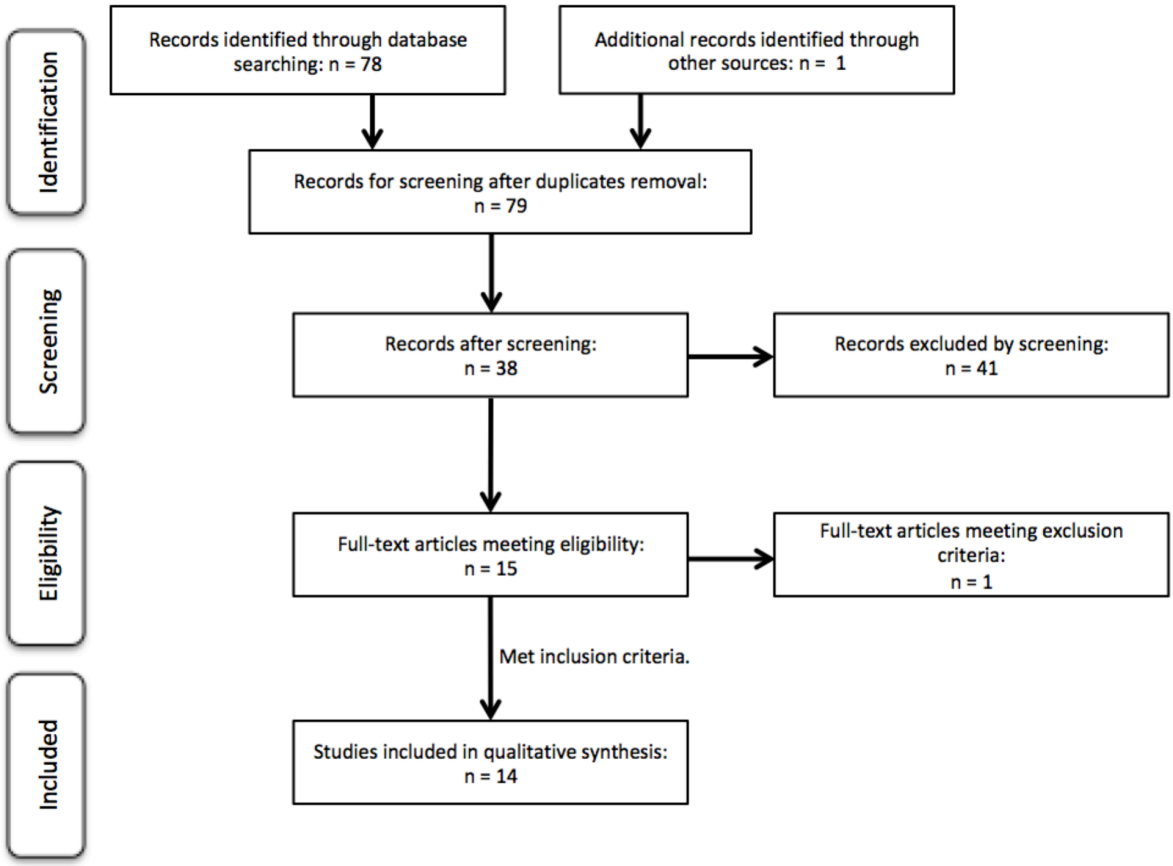
Additional analyses:

This review is **qualitative** and no quantitative comparative analysis was performed due to the heterogeneity of the articles included in the review.

Results

Study selection:

The studies included in the review were selected as follows **(Diagram 2)**:



Exclusions made:
Screening excluded 41 trials, which did not meet the mentioned criteria.

Following selection of 15 articles after assessment of eligibility, one article was excluded. The article by Sridhar et al[9] was a randomized control trial, but unfortunately no mention of research ethics committee approval was made. In keeping with the ethics policy of this review the article was excluded.

Additional record from other sources:
An additional study was identified outside the database search from the literature review used when writing the protocol. This study was included for its exceptionally comprehensive information on a dosing protocol.

Results of individual articles:

The results of the individual articles included in the review are presented in the tables hereunder.

Infusions are indicated as being given as a "loading dose" in **mg/kg** *or in some instances no loading dose* and thereafter a "maintenance dose" intra-op ± post-op in either **mg/kg/hr** or **mg/min**.

Further elaboration on the evidence of these findings will be discussed later in this report.

The strength of evidence indicated in each instance was derived from the following table **(Table 1)**:[10]

Strength	Level	Design	Randomization	Control
High	Level 1	Randomized control trial (RCT)	Yes	Yes
		Meta-analysis of RCT with homogeneous results	No	
	Level 2	Prospective comparative study (therapeutic)	No	Yes
		Meta-analysis of Level 2 studies or Level 1 studies with inconsistent results	No	
	Level 3	Retrospective Cohort Study	No	Yes
		Case-control Study	No	Yes
		Meta-analysis of Level 3 studies	No	
	Level 4	Case Series	No	No
	Level 5	Case Report	No	No
		Expert Opinion	No	No
Low		Personal Observation	No	No

Summary of results of individual studies (Table 2):

Article:	Strength of evidence:	Qualitative findings:	Safety:	Dosing:	Surgery (Disciplines):
Naik et al. [11] 2017	3	Retrospective cohort of lignocaine IVI alone vs. lignocaine IVI with ERAS − does the addition of ERAS protocol make lignocaine IVI more effective? Overall inconclusive results. Decreased opioid consumption in ERAS group, but intrathecal opioids were given. Pain scores higher in lignocaine alone group on POD1, but non-inferior from POD2 onward. Recommend lignocaine with ERAS.	Higher percentage of sedation/confusion in lignocaine group.	Fixed rate at 2-3mg/min intra-op. From recovery for 2-5 days post-op at 0.5-1mg/min.	GIT/abdominal surgery.
Terkawi et al. [12] 2016	3	Retrospective cohort where IVI lignocaine investigated as alternative to epidural. Non-inferior for pain scores from POD2, but inferior for opioid consumption. No worse adverse effects and prevents epidural adverse effects. Lignocaine an alternative to epidural, but supplement analgesia on POD1.	Minor adverse effects and one patient with a transient arrhythmia.	Fixed rate at 2-3mg/min intra-op. From recovery for 2-5 days post-op at 0.5-1mg/min.	GIT/abdominal surgery. Gynae surgery.
Kranke et al. [3] 2015	1	Systematic review of lignocaine vs. placebo/epidural. Individual trials not robust and inadequately powered − low quality evidence for use vs. placebo with reduced pain scores in first 8 hours post-op. No evidence for use over epidural.	Limited data on adverse effects.	No specific dosing protocol. Started intra-op and continued post-op.	GIT/abdominal surgery.
Bakan et al. [13] 2014	1	Prospective double blind RCT of Lignocaine, Dexmedetomidine, Propofol TIVA vs. Fentanyl, Remifentanil, Propofol TIVA. Evidence for lignocaine in conjunction with Dexmedetomidine as opioid free alternative by reduced opioid consumption in first 6h post-op.	Prolonged emergence in lignocaine group in PACU − likely due to Dexmedetomidine. No toxicity found.	Loading dose of 1.5mg/kg at induction. IVI intra-op at 2mg/kg/hr. Dexmedetomidine loading 0.6mcg/kg then 0.3mcg/kg/hr.	HPB surgery − specifically laparoscopic cholecystectomy.
Dewinter et al. [14] 2014	5	Protocol for lignocaine IVI vs. epidural. Included for its literature review. Mentions that lignocaine is an attractive alternative to epidural as well as opioid-based anaesthesia due to reduced adverse effects and fewer contra-indications.	Recommend that loading dose of 1.5mg/kg then IVI at 1.5mg/kg/hr used - found to have plasma levels <5mcg/ml. ECG monitoring should be considered.	Loading dose of 1.5mg/kg then IVI maintenance at 1.5mg/kg/hr.	GIT/Abdominal surgery mentioned.
Tikuisis et al. [15] 2014	1	Prospective double blind RCT of lignocaine IVI combined with fentanyl infusion IVI for 24h post-op vs. only lignocaine bolus at induction with placebo and fentanyl IVI post op. Lignocaine found to be superior to placebo in reducing pain scores and rescue analgesia requirements.	No mention of safety concerns or adverse effects.	Loading dose of 1.5mg/kg then IVI at 2mg/kg/hr intra-op and continued at 1mg/kg/hr post op with fentanyl at 0.1mcg/kg/hr for 24h post-op.	GIT surgery − specifically laparoscopic colon resection.
Bryson et al. [16] 2010	1	Prospective double blind RCT of lignocaine IVI vs. placebo to reduce length of hospital stay and post-op pain. No difference in opioid consumption, thus no benefit in using lignocaine, but both groups received comprehensive non-opioid adjuncts. Only trial where lignocaine was not better than placebo.	Intra-op lignocaine level determined to be well below toxic threshold of 5mcg/ml. Subjective symptoms of "toxicity" were actually higher in placebo group.	Loading dose of 1.5mg/kg then IVI at 3mg/kg/hr intra-op and discontinued at the end of surgery.	Lower abdominal GIT surgery. Gynae - Abdominal hysterectomy specifically.

Article:	Strength of evidence:	Qualitative findings:	Safety:	Dosing:	Surgery (Disciplines):
Yardeni et al. [17] 2009	1	Prospective double blind RCT of lignocaine and PCEA vs. placebo and PCEA to reduce pain and inflammatory markers. Lignocaine infusion resulted in lower pain scores at 4 and 8 hours, as well as lower inflammatory markers than placebo, when combined with PCEA.	At time of this article the safety profile was not yet established for post-op infusions, thus it was only given intra-op.	Loading dose of 2mg/kg at induction and then IVI at 1.5mg/kg/hr. (First trial with inverse dosing, i.e.: high loading dose with lower maintenance.	Gynae − Abdominal hysterectomy specifically.
Clarke et al. [18] 2008	4	Case series of three patients for who regional technique could not be provided and GA with lignocaine IVI given as alternative. Post-op pain scores, PCA use and LOS was shorter than expected for their respective surgeries.	Dose given regarded as safe from various other literature.	Fixed dose of 4mg/min IVI after a variable loading dose.	Orthopaedic − humerus surgery. HPB − laparoscopic cholecystectomy.
McCarthy et al. [19] 2010	1	Systematic review of RCTs to investigate lignocaine IVI as a adjunct vs. opioids or CEA to reduce post-op pain and length of recovery. Lignocaine IVI effective to reduce pain scores and opioid consumption, as well as enhance recovery, in sub-group of patients undergoing abdominal GIT surgery and open prostatectomy. Not effective for athroplasty, hysterectomy beyond 12h post-op, CABG or tonsillectomy.	No difference in sedation. Only one patient had asymptomatic levels > 5mcg/ml. Stable arrhythmia and bradycardia could occur.	Loading: 1.5mg/kg then IVI at 1.5-3mg/kg/hr. or 2-3mg/min. Regime with lignocaine IVI at 1mg/min post op and no loading dose was ineffective.	GIT/abdominal − effective. Not effective in: - hysterectomy - athroplasty - CABG - tonsillectomy
Dewinter, Moens et al. [20] 2017	1	Prospective double blind RCT of lignocaine IVI vs. placebo as part of multi-modal analgesia in reducing post-op pain following spinal arthrodesis. Non-statistically significant difference in opioid consumption − thus lignocaine not effective as an adjunct to multi-modal analgesia for spinal arthrodesis.	Liver and renal dysfunction mentioned as contraindications. Recommends ECG monitoring.	Loading dose of 1.5mg/kg at induction then IVI at 1mg/kg/hr till 6h post-op.	Neuro surgery/ Orthopaedic − specifically spinal arthrodesis.
Sun et al. [21] 2012	1	Systematic review and meta-analysis of RCTs to investigate lignocaine IVI vs. placebo for analgesia following abdominal surgery. Lignocaine IVI was effective in reducing pain scores as well as opioid consumption for first 24 hours post op.	Most trials reported no adverse effects. One trial reported one stable arrhythmia and another a 10% rate of headache.	Loading dose of 1.5-2mg/kg or 100mg then IVI at 1.5-3mg/kg/hr for various durations post-op.	Abdominal/GIT − colonic surgery. HPB − cholecystectomy.
Zhu et al. [22] 2017	N/A	Systematic review of adjunctive analgesics in paediatric perioperative analgesia: No articles regarding lignocaine met the inclusion criteria.	N/A	N/A	Paediatric surgery: no articles found regarding use.
Eipe et al. [4] 2016	3	Clinical audit from 3 years of lignocaine use in acute pain service. Use of lignocaine showed reduced pain scores and reduced opioid consumption. Recommended for use in potential or established acute hyperalgesia as part of a multi-modal regime − also effective as a bail-out analgesic for failed block or EA. Improved ERAS outcomes.	Mild side effects reported in 6/102 patients where infusion continued at lower dose or stopped. Does not require ECG monitoring and can give IVI in general ward. Assess clinically for sedation.	Loading dose of 1-2mg/kg at induction then 1-2mg/kg/hr IVI for 2-3 days. Stresses importance of bolus dose. Context sensitive half-time of ±20-40 min after 3 day infusion.	Neuro/orthopaedic − spine surgery. Other orthopaedic. GIT/abdominal surgery. Gynae − specifically hysterectomy.

Risk of bias within studies:

Selection bias
The five randomized control trials included in this review employed adequate randomization methods and the groups compared were in each case not statistically different and well matched. Thus there was little risk of selection bias.

Performance bias
One randomized control trial (Bakan et al.) compared more than one drug in their trial and even though blinding was adequate, the results could potentially not be attributed to the drug of interest in this review.

Detection bias
In the randomized control trials double blinding was used to adequately reduce the risk of detection bias. Likewise it was limited in the observational studies by a rigorous study method. In the case series by Clarke at al., as well as the clinical audit by Eipe et al., no blinding was possible and neither of these articles was written according to a guide or protocol. This could have led to bias in the observations made in those articles.

Attrition bias
Withdrawal of participants was minimal in few of the randomized control trials. There is a low risk of attrition bias.

Reporting bias
The randomized control trials, systematic reviews, retrospective cohorts as well as the clinical audit included in this review reported comprehensively on all outcomes – irrespective of statistical significance. The case series reported primarily on their significant findings in a subjective context. The research protocol included primarily positive literature to support the use of the intervention and rationale for their study. These articles that reported less consistently on all possible aspects of the intervention are inherently less relevant to the outcome of the review as indicated by a low strength of evidence.

Overall the risk of individual biases of articles was variable. Fortunately the greater the risk of bias, the lower the level of recommendation (strength of evidence) was.

Discussion

Summary of evidence:

This review was done in a qualitative capacity to increase the number of articles that could be included from the search strategy. Fourteen trials were included in this review of which eight offer level 1-strength of recommendation. Only two trials are of level 4 and 5 recommendation. The risk for bias is minimal due to the fortunate occurrence that trials that have better underlying methodology, reducing chance of bias, have better strength and are indicated as such. Therefore we have good confidence in the findings from our review, because of the good scientific basis of the majority of the articles included herein.

With regards to answering our research question, we will briefly discuss the findings under the three outcomes sought by the review.

1. General findings:

Advantages and disadvantages of using IVI lignocaine for peri-operative analgesia:

The mechanism of lignocaine IVI when used as a systemic analgesic is still unclear, but it may be attributed to sodium channel blocking in neural tissue at the site of injury. [4]

Investigations of lignocaine IVI compared to placebo conferred varying degrees of evidence to support its use on POD1 (post operative day 1), specifically in the first 4-8 hours post-op. [3, 15, 17, 20, 21.] In articles where lignocaine was used, vs. placebo of saline, in combination with other analgesic modalities such as PCEA (Patient Controlled Epidural Analgesia)[17] or fentanyl infusion[15], significant reduction in post-operative pain scores, opioid consumption and use of rescue analgesia was reported. Other articles where lignocaine was used, solely vs. placebo, reported no benefit – specifically in abdominal hysterectomy[16] and spinal arthrodesis (where opioid consumption was similar in both groups).[20] By contrast other trials reported good results from lignocaine IVI in hysterectomy surgery, but it again formed part of a multi modal regime.[4, 12, 17.] This suggests a benefit in using lignocaine as an adjunct to other modalities, rather than a sole analgesic option.

When lignocaine IVI was compared to conventional analgesic modalities such as CEA (Continuous Epidural Analgesia)[12] or ERAS (Enhanced Recovery After Surgery) protocol including lignocaine[11], there seems to be a benefit from POD2 (Post operative day 2) seen in reduced pain scores, though opioid consumption was higher in the lignocaine groups. This can be accounted for by the administration of intrathecal opioids when CEA was used either alone or in ERAS protocol. These findings are from retrospective cohorts and more robust prospective trials may be required to investigate the claims. However, the recommendation from the current evidence is that lignocaine forms an important component of ERAS, and those ERAS protocols should be used. If ERAS

protocol cannot be used, lignocaine IVI as an alternative could be effective from POD2 and supplemental analgesia should be given on POD1.

Many of the trials reported on improvement of secondary outcomes such as reduced ileus, PONV, length of stay and inflammatory markers. Most of the higher-level articles concluded favorable improvement in these aspects. [3, 4, 12, 13, 17, 19, 21] Trials that did not report any benefit on primary outcome, had the same conclusion for secondary outcome. [16, 20]

The reported disadvantages of using lignocaine IVI, aside from having no effect as mentioned above, include increased levels of sedation whilst on the infusion[11] as well as slower recovery times in the PACU (Post Anaesthetic Care Unit)[13]. This could make it undesirable as an analgesic where rapid, clear recovery is essential such as following neurosurgery.

Safety aspects regarding use of lignocaine IVI:

Overall the impression is that lignocaine IVI is safe to use for intra-operatively as well as prolonged infusions with no major adverse effects reported in any of the articles reviewed. The majority of nervous system adverse effects reported were minor sensory disturbances and sedation in a small subset of patients. [4, 11]
Cardiovascular effects were limited to stable arrhythmias (not specifically defined) and one stable bradycardia. [19, 21] In these instances the infusion was discontinued or continued at a lower dose. Continuous ECG monitoring is recommended in all articles except the audit by Eipe et al., where IVI lignocaine was given on general wards without monitoring other than sedation level and routine vitals.[4] Initially there was great concern for toxicity and older articles report early discontinuation of infusions because safety was not well established.[17] Trials measuring the blood levels of lignocaine during infusions support the more recent claims of safety by Eipe et al. – where in three trials only one patient had a level greater than 5mcg/ml and the patient was asymptomatic. [14, 16, 19]

Dosing protocols and safe infusion ranges:

Most protocols suggest a loading dose of 1-1.5mg/kg at induction of anaesthesia. Thereafter infusion rates as low as 1mg/kg/hr to as high as 3mg/kg/hr are recommended, with most articles reporting a rate of 1.5-2mg/kg/hr. As mentioned these infusions were given with no major adverse effects or safety concerns.
Regarding the duration of infusion, it can be safely given for 2-3 days post-op, with a relatively fast termination of effect owing to a context sensitive half time of 20-40 minutes after 3 days infusion. [4] A loading dose is recommended because equilibration time may be 4-8 hours and this must be borne in mind when changing the infusion rate once established. [4]
Contraindication to lignocaine infusion was reported where there were concerns of hepatic or renal insufficiency. [14]

As with any treatment the risk benefit ratio must be considered and good clinical judgment observed. Where the potential for toxicity is increased due to advanced age or organ dysfunction, this modality would best be withheld where other safer options are viable in such a context.

2. Surgeries where the use of IVI lignocaine has been investigated:

The literature ***supports the use*** of IVI lignocaine in the following surgeries

- Abdominal surgery: GIT and colon resection – good evidence (Supported by majority of articles)
- Hepatobiliary surgery: laparoscopic and open cholecystectomy – good evidence
- Urology: Laparoscopic or open prostatectomy – good evidence
- Gynecology: Hysterectomy – moderate evidence
- Neurosurgery: Spine surgery – mixed evidence
- Orthopaedic: Hip athroplasty, humerus ORIF – mixed evidence

The literature ***does not support*** the use of IVI lignocaine in the following surgeries

- Cardiac: CABG surgery – poor evidence for use
- Ear, nose and throat: Tonsillectomy – poor evidence for use

3. Surgeries that have not yet been investigated for the peri-op use of IVI lignocaine:

- Paediatric surgery: Single review done – no studies found for its use
- Plastic surgery
- Vascular surgery
- Breast and endocrine
- Thoracic surgery

Limitations:

Due to the academic context of this review it was limited to one search database and the search terms structured to include fairly recent and relevant articles in an international language. Inherent to this methodology is the risk that there were articles published that fell outside the search strategy and is therefore "missed". However, since meta-analysis were included, it is very likely that little literature was excluded.

Additionally, though the qualitative nature of this review increased the number of articles included, it would make the observations and conclusions somewhat subjective.

Finally, there is a fair amount of heterogeneity between the articles included and many of those articles included in the review have a degree of heterogeneity in their own source material. This further amplifies the uncertainty of some of the findings and claims reported in this review.

Conclusions

It is clear that IVI lignocaine is an attractive addition to analgesia in the peri-operative period in certain subsets of patients. There is adequate literature to support its use in especially abdominal surgery where visceral pain predominates. It has an accepatable safety profile and seems to offer more benefit than harm when used appropriately. Currently the literature is skewed by randomized control trials in only a few surgical populations and meta-analysis of such studies indicate heterogeneity in the results. Additionally the criteria for "non-statistical significance" were arbitrarily defined, which may exclude actual clinically significant evidence solely based on this margin.

In conclusion, lignocaine IVI could form part of a comprehensive multi-modal analgesic regime for surgeries associated with visceral pain. Its role becomes even more important when interventional modalities of opioid sparing anaesthesia is contraindicated – such as instances where a CEA or peripheral nerve block cannot be safely performed or has failed. This is also true when systemic non-opioid analgesics such as NSAIDs are contraindicated. Contraindication for the use of lignocaine is only mentioned in the setting of liver or renal failure and known hypersensitivity. When used in the appropriate context, it seems that it is superior to placebo on POD1 and non-inferior to interventional analgesics such as CEA from POD2. Thus it should be supplemented on POD1 with other analgesics, which can then be tapered from POD2, to gain the benefit of using lignocaine IVI.

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Chapter 3:

Recommendation for further research and application of findings

Recommendation for further research:

The review of the literature highlighted two main concerns in the context of further research. Firstly, it is not well defined in the literature how to quantify non-inferiority statistically, when comparing lignocaine IVI with other established analgesic regimes. Articles investigating non-inferiority reported the requirement of less than 1-point difference on the 11-point numerical visual analog pain scale, or a mean odds ratio of opioid consumption less than 1.2, to be non-inferior. Though pain scores in the intervention groups were lower in most articles, it did not meet this criterion for non-inferiority. Additionally the mean odds ratio of opioid consumption yielded inconclusive results. This begs the question whether lignocaine is truly inferior by comparison or if our margin to achieve non-inferiority is too narrow?

Secondly, as also mentioned in the limitations of this review, heterogeneity amongst the articles in this review as well as other reviews are of concern.

To solve these issues a consensus needs to be found on how to define non-inferiority in this context and robust prospective double blind randomized control trials need to be performed. Furthermore the surgical disciplines identified by this review to be lacking any substantial literature regarding the use of IVI lignocaine for analgesia should be the focus of future investigation. Bearing in mind the beneficial effects seen on visceral pain in abdominal surgery, thoracic surgery could be an exciting avenue to consider in future trials.

Application of findings:

Any changes in clinical practice stemming from this review will only be considered after it has been reviewed for marking and subsequently peer reviewed during the application for publication. Publication will be sought in the Southern African Journal of Anaesthesia and Analgesia (SAJAA). Should this manuscript be published it would reach a wide audience of practitioners to guide the use of IVI lignocaine, the context in which it is appropriate as well as give direction to future research endeavors.

Appendices

- Data collection device **Appendix A**
- Reference list sheet **Appendix B**
- Cochrane risk of bias tool **Appendix C**
- PRISMA checklist for writing the report **Appendix D**
- Ethics clearance letter **Appendix E**
- Free State DOH approval letter **Appendix F**

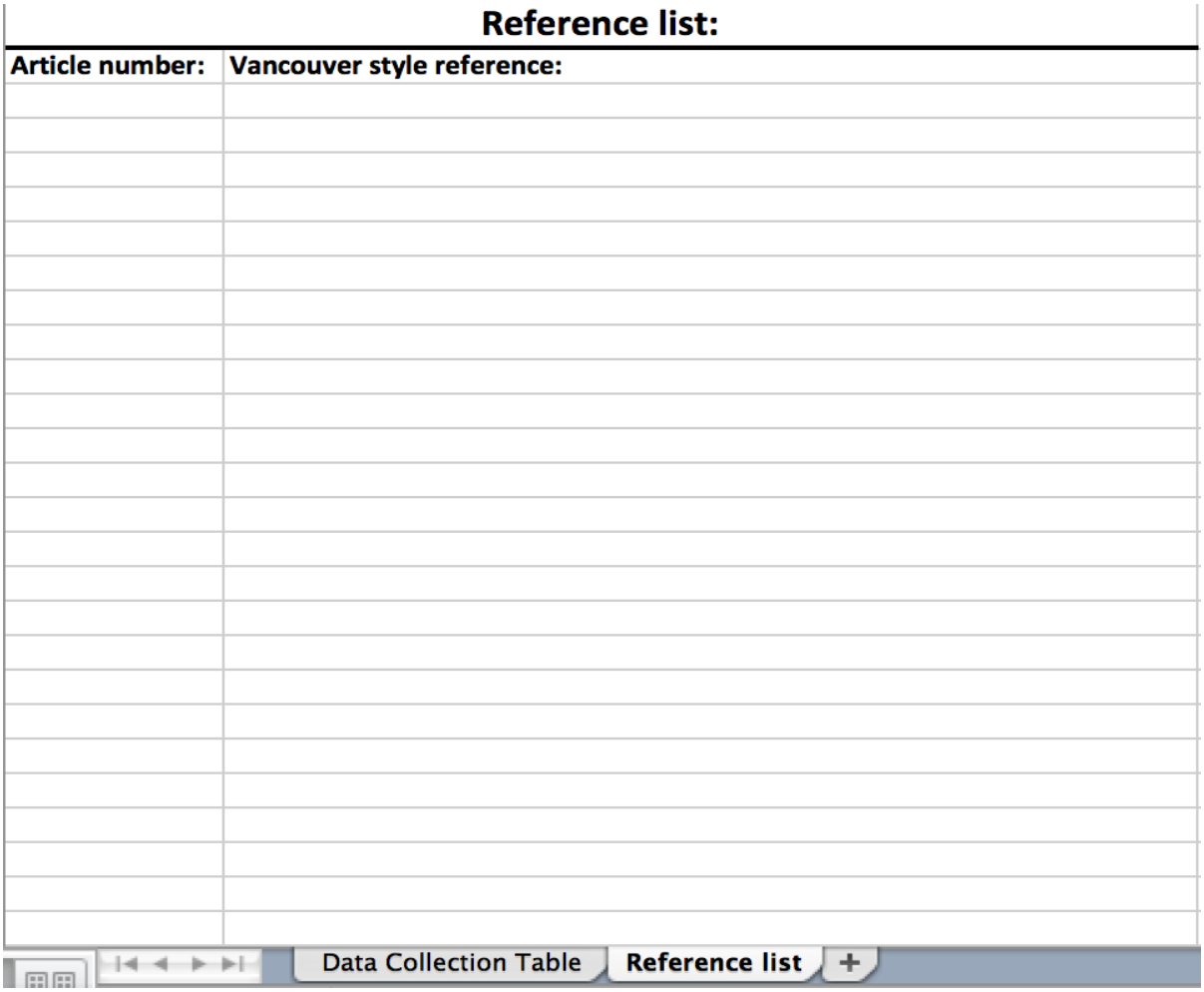
Appendix A: Data collection device

Data collection table - Lignocaine systematic review:	
Outcome 1: General findings and safety	
1.1. Advantages of lignocaine IV mentioned:	**Article number:**
1.2. Disadvantages of lignocaine IV mentioned:	**Article number:**
1.3. Safety mentioned:	**Article number:**
1.4. Dosing protocols mentioned:	**Article number:**
Outcome 2: Specific disciplines mentioned	
2.1. Neuro surgery mentioned:	**Article number:**
2.2. Plastic surgery mentioned:	**Article number:**
2.3. Orthopaedics mentioned:	**Article number:**
2.4. Vascular surgery mentioned:	**Article number:**
2.5. HPB surgery mentioned:	**Article number:**
2.6. Gastro surgery mentioned:	**Article number:**
2.7. Mamma and endocrine surgery mentioned:	**Article number:**
2.8. Paeds surgery mentioned:	**Article number:**
2.9. Thoracic surgery mentioned:	**Article number:**
2.10. Cardaic surgery mentioned:	**Article number:**
2.11. Urology mentioned:	**Article number:**
2.12. ENT mentioned:	**Article number:**
2.13. Obs/Gynae mentioned:	**Article number:**

Outcome 3: Disciplines not mentioned or specified as not investigated				
	Not mentioned			
	Yes		**Mentioned but exluded:**	**Article number:**
			Reason?	
3.1. Neurosurgery				
3.2. Plastic surgery				
3.3 Orthopaedic surgery				
3.4. Vascular surgery				
3.5. HPB surgery				
3.6. Gastro surgery				
3.7. Mamma and endocrine				
3.8. Paeds surgery				
3.9. Thoracici surgery				
3.10. Cardaic surgery				
3.11. Urology				
3.12. ENT				
3.13. Obs/gynae				

Data Collection Table | Reference list | +

Appendix B: Reference list



Reference list:	
Article number:	**Vancouver style reference:**

Data Collection Table | **Reference list** | +

Appendix C: Cochrane risk of bias assessment tool

The Cochrane Risk of Bias Tool

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias		
Blinding of participants and personnel. Assessments should be made for each main outcome (or class of outcomes).	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias		
Blinding of outcome assessment. Assessments should be made for each main outcome (or class of outcomes).	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias		
Incomplete outcome data. Assessments should be made for each main outcome (or class of outcomes).	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

Appendix D: PRISMA checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

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Appendix E: Ethics clearance letter

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

22-Feb-2018

Dear **Dr Johannes Vorster**

Ethics Clearance: **Intravenous lignocaine for perioperative analgesia – a systematic review identifying current applications and future potential.**

Principal Investigator: **Dr Johannes Vorster**

Department: **Anaesthesiology (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2017/1451**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
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Appendix F: Free State DOH approval letter

health
Department of Health
FREE STATE PROVINCE

05 February 2018

Dr JG Vorster
Department of Anaesthesiology
Faculty of Health Science
UFS

Dear Dr JG Vorster

Subject: Intravenous lignocaine for perioperative analgesia – a systematic review identifying current applications and future potential.

- Please ensure that you read the whole document, Permission is hereby granted for the above – mentioned research on the following conditions:
- Participation in the study must be voluntary.
- A written consent by each participant must be obtained.
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of Universitas Hospital nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** sebeelats@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- Please discuss your study with the institution manager/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.
Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 9/02/18

Head : Health
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