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The effectiveness of topical bupivacaine application versus placebo in managing pain in paediatric and adult adenotonsillectomy patients: a systematic review & metaanalysis

Desai, Shainal

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The effectiveness of topical bupivacaine application versus placebo in managing pain in paediatric and adult adenotonsillectomy patients – a systematic review & meta-analysis

Dr. Shainal Desai

A research report submitted to the Faculty of Health Sciences,

University of the Witwatersrand, Johannesburg,

in the partial fulfilment of the requirements for the degree of

Master of Medicine in the branch of Anaesthesiology

Johannesburg, 2021

Declaration

I, Shainal Desai, herewith declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



_____

Signed

On this 09 day of November 2021

Dedication

This research project is dedicated to my family who have always provided unwavering support in all my endeavours. It is also dedicated to my loving wife who has always motivated me since I began this journey.

Presentations and publications from this research project

1. This article has been submitted to SAMJ and is currently under review. Manuscript number - SAMJ15775.

Abstract

Background: There is a high incidence of severe post-operative pain experienced by patients undergoing adenotonsillectomies. During this procedure, there is often a need for local anaesthetic use which has minimal side effects, is cost effective and is easy to administer. Bupivacaine is a long acting and potent local anaesthetic that is widely available in resource constrained settings. Its topical application into the tonsillar fossa could provide sufficient analgesia whilst avoiding complications seen with its infiltrative technique.

Objective: To determine the efficacy of topical bupivacaine in the management of post-adenotonsillectomy pain compared to placebo using data from randomised controlled trials (RCTs).

Methods: This systematic review and meta-analysis was registered with PROSPERO (CRD42020180502) and adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines. A comprehensive search of the scientific literature was conducted on PubMed, Scopus and the Cochrane Library online databases. RevMan 5.4 software was used for statistical analysis. The risk of bias and quality of the studies included was determined using the Cochrane Risk of Bias (ROB) Tool Version 2.

Results: Seven studies out of 58 were included in the systematic review with a total of 406 patients. Six of these studies had investigated post-operative pain scores for tonsillectomy alone. Three of the studies showed low risk of bias, three had some concerns and one was at high risk of bias. Topical bupivacaine produced a significant reduction in pain score estimates at 1-hour [−2.32 (95% CI: −3.98; −0.66)], 4-hours [−2.93 (95% CI: −5.05; −0.81)] and 5-6-hours [−1.73 (95% CI: −3.15, −0.30)] (standardised mean differences) post-adenotonsillectomy when compared to placebo. The analysis also reports no complications associated with use of topical bupivacaine. The dose of bupivacaine was 0.5% for six of the seven studies, and 0.25% for the one study. The included trials varied according to volume and duration of application of bupivacaine. There was significant heterogeneity in the analysis undertaken.

Conclusion: Topical bupivacaine was effective and safe in reducing post-adenotonsillectomy pain scores up to 6 hours post-operatively. This method of administration is ideal in resource

constrained environments as it avoids potentially serious complications that are associated with the infiltration technique.

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I would like to thank Dr Sithandiwe Dingezweni for all his support and hard work in aid of completion of this project. I would acknowledge Dr Yoshan Moodley for guiding me through the processes involved in research. I would like to thank Prof Palesa Motshabi for always availing herself to my numerous questions and for showing a steadfast belief in me. To Renisha Desai for always being willing to read my drafts and provide feedback.

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List of abbreviations

RCT	Randomised controlled trial
PICO	Problem/population, Intervention, Comparison, and Outcome
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analysis
ROB	Risk of Bias
SMD	Standardised mean difference
MD	Mean difference
VAS	Visual Analogue Scale

Draft Article

This article is prepared in accordance with the author guidelines (Appendix 5) as stipulated by the South African Medical Journal (SAMJ) and may differ from the rest of the document.

The effectiveness of topical bupivacaine application versus placebo in managing pain in paediatric and adult adenotonsillectomy patients – a systematic review & meta-analysis

Authors
Shainal Desai [1¶], Sithandiwe Dingezweni [1&], Yoshan Moodley [1&], Palesa Motshabi Chakane[1&]

Institution
[1.] Department of Anaesthesiology, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand

Orchid ID
https://orcid.org/0000-0001-6757-3290

Corresponding author
Charlotte Maxeke Johannesburg Academic Hospital, Department of Anaesthesiology
7 York Road, Parktown, 2193
Contact number: 082 770 8326
Email: Shainal.desai@gmail.com

[¶]This is the main author.
[&]These authors contributed equally to this work in a supervisory capacity.

Abstract

Background: There is a high incidence of severe post-operative pain experienced by patients undergoing adenotonsillectomies. During this procedure, there is often a need for local anaesthetic use which has minimal side effects, is cost effective and is easy to administer. Bupivacaine is a long acting and potent local anaesthetic that is widely available in resource constrained settings. Its topical application into the tonsillar fossa could provide sufficient analgesia whilst avoiding complications seen with its infiltrative technique.

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Results: Seven studies out of 58 were included in the systematic review with a total of 406 patients. Six of these studies had investigated post-operative pain scores for tonsillectomy alone. Three of the studies showed low risk of bias, three had some concerns and one was at high risk of bias. Topical bupivacaine produced a significant reduction in pain score estimates at 1-hour [−2.32 (95% CI: −3.98; −0.66)], 4-hours [−2.93 (95% CI: −5.05; −0.81)] and 5-6-hours [−1.73 (95% CI: −3.15, −0.30)] (standardised mean differences) post-adenotonsillectomy when compared to placebo. The analysis also reports no complications associated with use of topical bupivacaine. The dose of bupivacaine was 0.5% for six of the seven studies, and 0.25% for the one study. The included trials varied according to volume and duration of application of bupivacaine. There was significant heterogeneity in the analysis undertaken.

Conclusion: Topical bupivacaine was effective and safe in reducing post-adenotonsillectomy pain scores up to 6 hours post-operatively. This method of administration is ideal in resource constrained environments as it avoids potentially serious complications that are associated with the infiltration technique.

Keywords:
Adenotonsillectomy, topical bupivacaine, analgesia, post-operative pain

Introduction

Tonsillectomies are one of the most regularly performed surgeries around the world [1]. International cross sectional and randomised controlled trials estimate that severe post-operative pain is reported in as many as 25–50% of children and 14.5% of adults [2-4]. This factor contributes toward morbidity as patients often struggle to eat, drink, talk or sleep because of the severe pain [5-7]. Children are at a greater risk of additional complications such as behavioural alterations and vomiting [8].

Post-operative pain may lead to prolonged hospitalisation, increased requirement of supplementary analgesia, with subsequent experience of side effects and overall inferior treatment outcomes [7, 9]. Seshamani *et al*. [7], demonstrated that the average cost of an uncomplicated tonsillectomy in an adult was US$ 3 832. This cost increased by up to 80% if pain was experienced within the first 14 days post-surgery. Given that the majority of adenotonsillectomies are performed as elective day-case surgeries, an analgesic pain management plan which timeously allows patients to resume their daily activities is beneficial [10]. Local anaesthetics can be safely utilised to manage pain from adenotonsillectomies while still avoiding complications seen with the use of systemic supplementary analgesic agents [6].

Bupivacaine is a long-acting local anaesthetic that is widely available, and its use has been favoured over other agents, such as lidocaine and ropivacaine, owing to its higher relative potency and extended duration of action [11, 12]. The inherent risk of infiltrative local anaesthetic is higher than its topical application since the former requires the insertion of a needle and deposition of the drug into deeper tissue planes. This procedure has the potential to cause complications which are not seen with topical administration [6]. Examples of complications with local anaesthetic infiltration of the tonsillar fossa include: life threatening arrhythmias from accidental intravascular injection [13]; baroreceptor dysfunction (resulting in haemodynamic changes) and upper airway obstruction from unintentional blockade of the glossopharyngeal and vagus nerve [14]; visual loss, cervical osteomyelitis and bilateral vocal cord paralysis [15, 16]. It is beneficial that the ideal method of administration of bupivacaine should provide adequate analgesic effect and limit complications. This is exceptionally critical in constrained, overburdened, and under-resourced settings whereby any complication places additional pressure on available resources. This is true for most developing countries.

A critical analysis of systematic reviews conducted on similar studies indicates that although local anaesthetics do have a role in managing post-adenotonsillectomy pain, the exact method of application (topical or infiltrative) has not been described based on consistent evidence [6, 17-19]. Limitations of these reviews are that they are based on studies with small sample sizes, have a high risk of bias or do not focus on topical bupivacaine [6, 17-19]. A recent systematic review and meta-analysis, showed that local anaesthetics do have a role in reducing post-tonsillectomy pain and that topical administration appears to provide similar analgesic effects as infiltration [20]. The type and concentration of local anaesthetic was diverse among all the included studies thus, they were not able to obtain meaningful meta-analyses of individual agents and make recommendations on effective dosing [20]. An important consideration in their review is the fact that additional analgesic agents (such as ketamine, clonidine, fentanyl and pethidine) were used which may have concealed the true effect of the local anaesthetic and subsequently influenced final outcomes. This lack of consensus has made it challenging for surgeons and anaesthetists to safely incorporate local anaesthetics into their post-operative pain management plan for patients undergoing adenotonsillectomies.

This study was designed to investigate, in a systematic review, the use of topical bupivacaine application in comparison to placebo in patients undergoing adenotonsillectomies. The study would give information on a modality that is not only easily available in resource constrained environments, but one that is safe, economical, effective, and simple to administer.

Objectives

The objective of this study is to determine the efficacy of topical bupivacaine in the management of post-adenotonsillectomy pain compared to placebo using data from randomised controlled trials (RCTs). The search strategy was developed in accordance with the problem/population, intervention, comparison, and outcome (PICO) framework [21]. We described the population as patients undergoing adenotonsillectomy (paediatric and adult), the intervention as those receiving topical bupivacaine (all doses), the comparator as those receiving a placebo/saline and the outcome as the measured pain scores. All bupivacaine doses were included.

Methods

Protocol and registration

The present study protocol was registered with PROSPERO (CRD42020180502), and adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines [22].

Ethical approval

This research was approved by the University of the Witwatersrand's Research Ethics Committee (Reference number: W-CBP-200804-01).

Eligibility criteria

Abstracts of articles returned from the electronic medical literature database search were screened for eligibility using the following inclusion/exclusion criteria. The inclusion criteria for the review were as follows: 1) prospective, randomised controlled trials; 2) studies of patients (adults and children) who underwent either adenoidectomy or tonsillectomy, or both; 3) use of topical bupivacaine administration; 4) comparison of the effects of topical bupivacaine with a placebo; 5) availability of numerical data on post-operative pain scores/assessments for quantitative analysis. The exclusion criteria were as follows: 1) trials which did not report on any of the endpoints; 2) duplicate study/publication; 3) manuscripts not written in English; 4) studies in which a consistent anaesthetic protocol was not implemented.

Information sources, search and study selection

The following online databases were utilised: PubMed, Scopus and the Cochrane Library. These medical literature databases were searched from the inception of the databases until the date of search. The search was performed independently by two authors on the 6th of June 2020 (ShD and SiD) and included all papers to that date. A detailed list of search terms used in each database is shown in Appendix 1.

Data collection process

The search and review processes were carried out independently by two authors (ShD and SiD). The results from the database search were exported to a reference management tool and then onto two identical spreadsheets. The title and abstracts of the studies were screened according to the predefined inclusion and exclusion criteria. Where there was uncertainty about articles for inclusion input from other reviewers was sought (YM and PMC). In addition to the electronic database search, the reference lists of eligible articles and of systematic reviews found in the search were screened for relevant articles which might have been missed by the electronic database search. A full text review was performed to establish if these should be included in the review. The relevant endpoints were independently extracted into standardised data collection sheets by two of the authors (ShD and SiD). The extracted data was then compared to ensure accuracy.

Data items

The following data were extracted from the eligible articles:

- General study details: (a) authors, (b) year of publication, (c) country in which study was conducted.
- Participants: (a) sample size, (b) age groups, (c) male/female distribution, (d) operation – tonsil, adenoid or both removed, (e) surgical technique.
- Intervention: (a) dosage, (b) length of time in follow-up.
- Control: (a) type (b) length of time in follow-up.
- Outcomes: (a) reduction in pain scores (using validated scales), (b) post-operative analgesia, (c) complications experienced.

Risk of bias (quality) assessment

The risk of bias and quality of the studies included was determined using the Cochrane Risk of Bias (ROB) Tool Version 2 [23]. It is structured into a fixed set of domains of bias, focusing on different aspects of trial design, conduct, and reporting. Judgements can be 'Low' or 'High' risk of bias or can express 'Some concerns'. The five domains (D) include bias due to: randomisation (D1), deviations from intended intervention (D2), missing data (D3), outcome measurement (D4) and selection of reported result (D5). Robvis [24], an online tool, was used to create a summarised graphical representation of the assessment. Study quality was independently assessed by two authors (ShD and SiD). A third reviewer was consulted when a consensus could not be reached (YM).

Summary measures and synthesis of results

The statistical analyses were conducted using Review Manager Version 5.4 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020). All data was continuous in nature (i.e. pain scores) and its analysis was performed using the standardised mean difference (SMD) of estimates where there was heterogeneity, and mean difference (MD) of estimates with homogenous data. Between-study heterogeneity was assessed using the χ^2 test where $p < 0.10$ indicated presence of heterogeneity. The degree of heterogeneity was measured using an I^2 test, with $I^2 > 50\%$ indicative of a high level of heterogeneity. Where there was a significant degree of heterogeneity, random effects were reported, and fixed effects reported for a homogenous dataset. Individual forest plots were prepared for relevant

time intervals, with the accompanying 95% confidence intervals calculated. Statistical significance was set at $p < 0.05$.

Results

Study selection

Fig. 1 shows the PRISMA flow diagram detailing the process by which the final list of studies was derived for inclusion in this review. The search strategy of the three medical databases identified a total of 57 titles. Screening the reference list of the review compiled by Fedorowics *et al*. [17], yielded one additional relevant title [25]. Twenty-seven duplicate studies were then removed. There was a total of 31 studies screened thereafter. Reasons for exclusion of 20 articles included:

- Not RCT (2 manuscripts)
- No bupivacaine (7 manuscripts)
- No tonsillectomy, adenoidectomy, or both (6 manuscripts)
- Full text not available in English (1 manuscript)
- Not topical (4 manuscripts)

The full-text publications of 11 articles were subsequently reviewed. Thereafter 4 studies were excluded for the following reasons:

- Study incomplete - Registered protocol (1 manuscript)
- Not topical bupivacaine (1 manuscript)
- No formal pain scale (1 manuscript)
- No detailed quantitative data available (1 manuscript)

Therefore, this systematic review comprised 7 eligible manuscripts [13, 25-30]. Relevant data was extracted from these publications and their supplementary material.

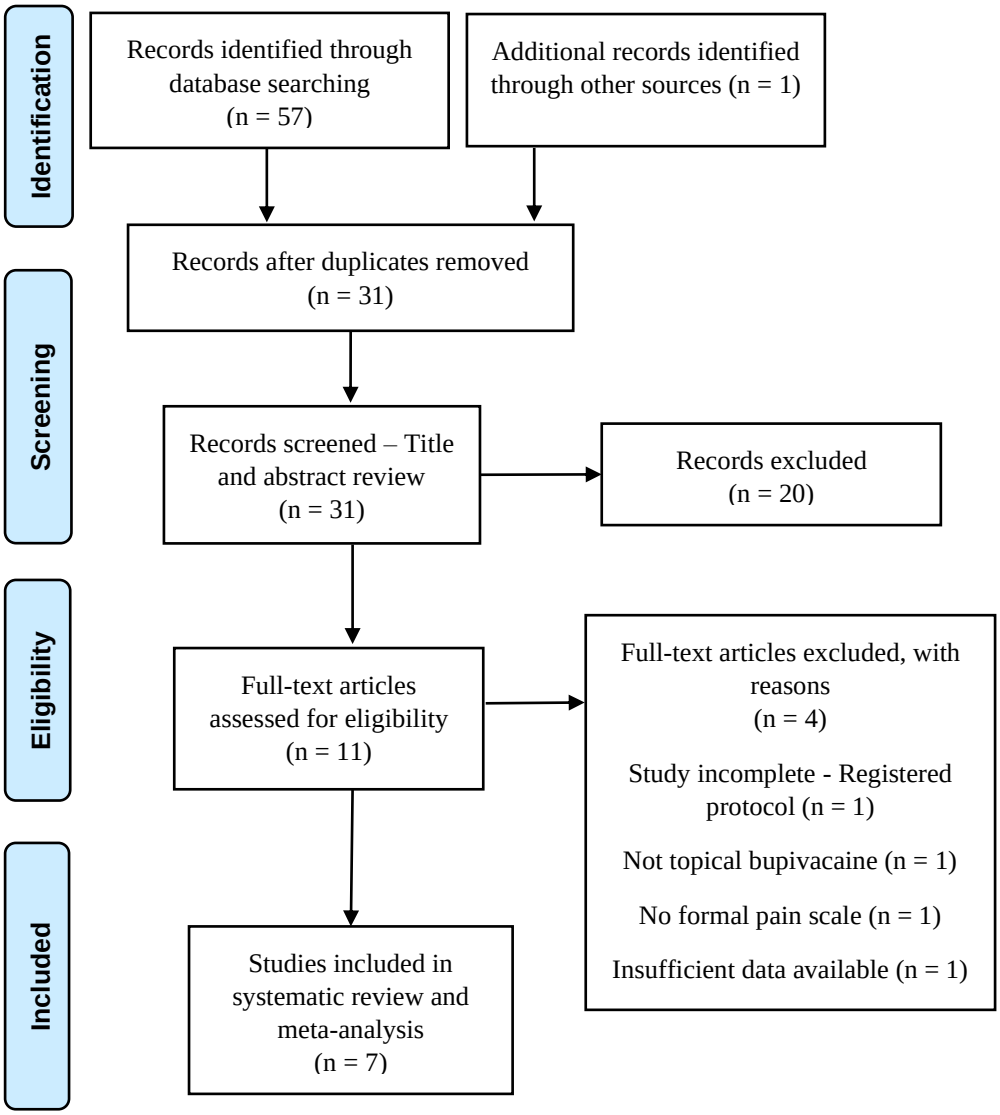


Fig. 1. PRISMA Flow Diagram.

Study characteristics of included studies

The characteristics of the seven included studies are represented in Table 1. Four of the included studies had allocated individual patients to either an intervention (topical bupivacaine) or control group (placebo) [25, 28-30]. The remaining three studies had adopted an 'intra-individual study design' whereby one tonsillar fossa received the intervention and the contra-lateral side the control [13, 26, 27]. The sample sizes of the studies varied from 35 to 99 participants with ages ranging from 1.5 to 53 years of age. The combined sample size of all the studies was 406 patients. There were more males included in the studies with a 51.76% distribution. Six of the included studies had patients who had undergone tonsillectomies alone. Only the study by Bukhari *et al.* [27], included 28 patients which had combined adenotonsillectomies carried out. Majority of the studies used cold dissection as their preferred surgical technique. The concentration of plain bupivacaine used was either 0.25% (2.5mg/ml) or 0.5% (5mg/ml) but the volume and duration of application varied among the studies. No studies used bupivacaine with epinephrine. All studies reported pain scores using a Visual Analogue Scale (VAS) or the McGrath's Face Scale.

Table 1. Characteristics of Included Studies

General Study Details		Participants					Intervention	Control	Outcome		
Author & year	Country	Sample size	Age	Male/female distribution	Operation	Surgical technique			Pain scores	Post-operative analgesia	Complications experienced
Bentur et al., 2015	India	50 people	8 - 30 years old; Mean age of 15	50% Male; 50% Female	Tonsillectomy	Cold dissection	Swab soaked with 1-3ml of 0.5% bupivacaine for 5 min	Swab soaked with saline for 5 min	Pain score (VAS) at 0, 0.5, 1, 2, 4, 6 and 8 hours post-operation	Not recorded	Nil reactions/ complications noted
Bukhari et al., 2012	Saudi Arabia	35 people	3 - 53 years old; Mean age of 10.3	66% Male; 34% Female	Tonsillectomy (n = 7) with adenoidectomy (n = 28)	Cold dissection & haemostasis by electrocautery as needed	Gauze soaked with 4ml of 0.25% bupivacaine for 5 min	Gauze soaked with saline for 5 min	Pain score (VAS) at 2, 4, 6, 12 and 24 hours post-operation	Not recorded	Nil reactions/ complications noted
Chaturvedi et al., 2005	India	70 people	8 - 35 years old	54.3% Male; 45.7% Female	Tonsillectomy	Cold dissection	Gauze soaked with 2ml of 0.5% bupivacaine for 3 min	Gauze soaked with saline for 3 min	Pain score (VAS) at 1, 2, 4 and 8 hours post-operation	Nil additional analgesia given to either group	Nil reactions/ complications noted
Haksever et al., 2014	Turkey	40 people	3 - 15 years old	50% Male; 50% Female	Tonsillectomy	Hot dissection (Bipolar forceps)	Swab soaked with 5ml of 0.5% bupivacaine for 2-3 min	Swab soaked with saline for 2-3 min	McGrath's Face Scale at 1, 5, 13 and 17 hours as well as 1, 2, 3, 4, 5 and 6 days post-operation	All patients received oral acetaminophen paediatric suspension (10–20 ml/kg) post-operatively	Nil reactions/ complications noted
Hung et al., 2002	United Kingdom	99 people	3 - 16 years old	53.5% Male; 46.5% Female	Tonsillectomy	Hot dissection (Bipolar forceps)	Swab soaked with 0.5% bupivacaine at 3mg/kg for 5 min	Swab soaked with saline for 5 min	Pain score (VAS) at 1, 3 and 6 hours post-operation	Patients received paracetamol (10.mg/kg) and codeine phosphate (3 mg/kg) according to a standard post-operative protocol	None of the 50 patients from the bupivacaine group reported any complications
Kadar et al., 2003	Pakistan	72 people	7 - 35 years old	37.5% Male; 62.5% Female	Tonsillectomy	Cold dissection. The bleeding was controlled by unipolar diathermy or ligation.	Swab soaked with 2ml of 0.5% bupivacaine for 5 min	Swab soaked with saline for 5 min	Pain score (VAS) at 4 hours post-operation, before bed, before breakfast, before lunch and before discharge.	Not recorded	Not recorded
Ozmen et al., 2011	Turkey	40 people	1.5 - 15 years old	47.5% Male; 52.5% Female	Tonsillectomy	Hot dissection (Bipolar forceps)	Swab soaked with 5ml of 0.5% bupivacaine (Duration not recorded)	Swab soaked with saline (Duration not recorded)	McGrath's Face Scale at 1, 5, 13, 17 and 21 hours as well as 1, 2, 3, 4, 5 and 6 days post-operation	All patients received oral acetaminophen paediatric suspension (10–20 ml/kg) post-operatively	Nil reactions/ complications noted

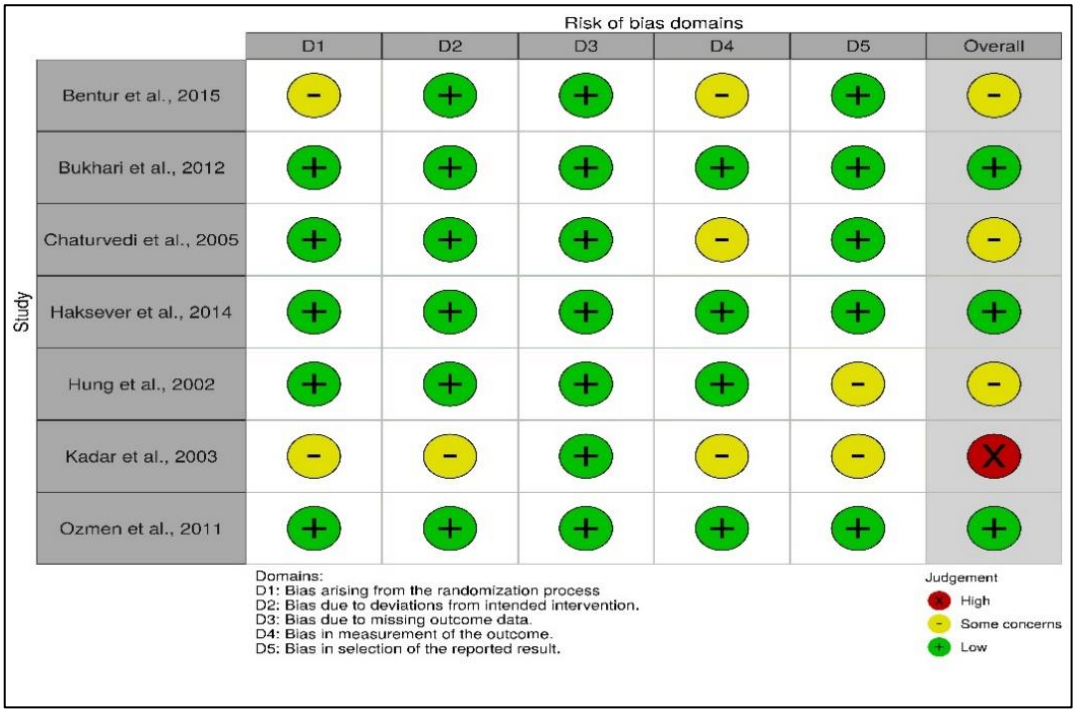
VAS, Visual Analogue Scale

n = number of patients

Risk of bias within and across studies

The outcomes of the ROB assessment are presented in Table 2. One study was evaluated as having a "High risk" of bias [13]. Three studies were judged to have "Some concern" [25, 26, 29]. The remaining studies had a "Low risk" of bias [27, 28, 30]. Two studies showed bias arising from the randomisation process [13, 26]. The impact of this is minimal as no evidence could be found that one tonsillar fossa is more prone to pain than the other, hence negating the impact of randomisation in these intra-individual designed studies. All the included studies showed low risk of bias with regards to missing outcome data as depicted in Fig. 2.

Table 2. Cochrane Risk of Bias Assessment of Studies



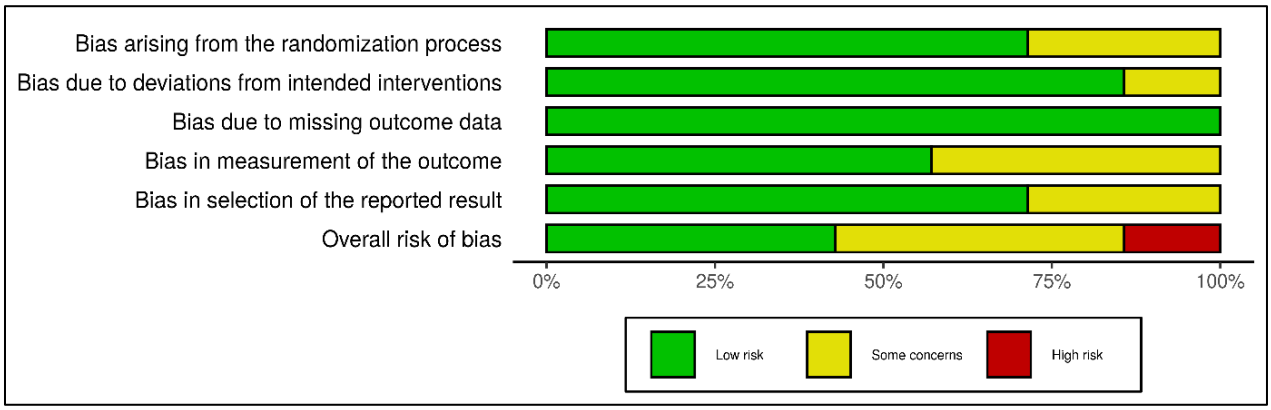


Fig. 2. Distribution of risk of bias judgements within each bias domain

Results and synthesis of individual study data

Due to the elimination half-life of bupivacaine which is approximately 210 minutes and a duration of action of 8 hours [31, 32], data points analysed included pain scores at 1, 2, 4, 5-6 and 8 hours post-adenotonsillectomy. All studies presented sufficient data for a meta-analysis of association with pain scores at these times.

Pain at 1-hour

Five studies recorded pain scores that could be compared at 1-hour post-tonsillectomy [25, 26, 28-30]. In comparison with placebo, pain score estimates at 1-hour post-operation was significantly lower in the topical bupivacaine group −2.32 [95% CI: −3.98; −0.66], (P = 0.006) (Fig. 3). The data however was significantly heterogeneous (P < 0.00001); I^2 = 97%.

Pain at 2-hours

Data from three studies were comparable at 2 hours post-tonsillectomy. The SMD of pain score estimates were equivocal between bupivacaine and placebo −2.82 [95% CI: −5.97; 0.32], (P = 0.08) (Fig. 4), and the measure of heterogeneity was (P < 0.00001); I^2 = 99%. Two of the 3 studies included in this meta-analysis used an intra-individual study design [26, 27].

Pain at 4-hours

The analysis of four studies indicated that the use of topical bupivacaine led to a significant reduction in pain scores estimates at this time interval [13, 25-27]. The SMD was −2.93 [95% CI: −5.05; −0.81], (P = 0.007), and the measures of heterogeneity using Chi^2 was significant (P < 0.00001); with I^2 = 98%, when placebo was compared to topical bupivacaine (Fig. 5). Seventy-five percent of this group had utilised an intra-individual study design.

Pain at 5-6 hours

Five studies assessed pain scores at a time interval 5–6 hours post-tonsillectomy [26-30]. Overall, compared with placebo, topical bupivacaine was favoured over placebo, with SMD estimates of −1.73 [95% CI: −3.15, −0.30] (P = 0.02) and significant heterogeneity is (P < .00001); I^2 = 97% (Fig. 6).

Pain at 8-hours

Two of the seven included studies provided sufficient data during the late post-operative period for inclusion in an 8-hour analysis [25, 26]. When compared with placebo, topical bupivacaine pain score estimates were not superior to placebo, SMD −4.41 [95% CI: −9.55, 0.74] (P = 0.09), with significant heterogeneity (P < .00001); I^2 = 99%, (Fig. 7).

Pain post 8 hours

Three studies had recorded pain scores at 24 hours and longer. However, an analysis was not deemed feasible as it extends beyond the duration of action of bupivacaine [31, 32].

Additional analgesia requirements

Three studies did not record additional analgesia usage [13, 26, 27] and three used standardised post-operative analgesia protocols [28-30]. In one study no systemic analgesics were given to either group for the first 24 hours after surgery after which patients were then discharged with no record kept [25]. No studies verified that additional analgesia was required in the control groups.

Adverse events

Majority of the studies reported that there were no complications noted [25-30]. Only one study had not explicitly mentioned or recorded post-operative complications [13].

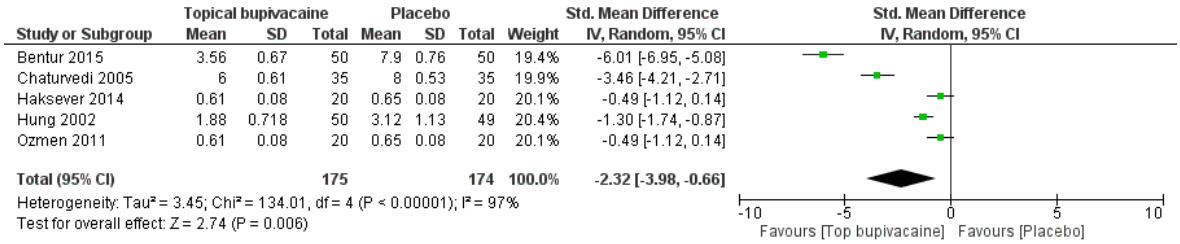


Fig. 3. Meta-analysis of pain scores 1-hour post-operation

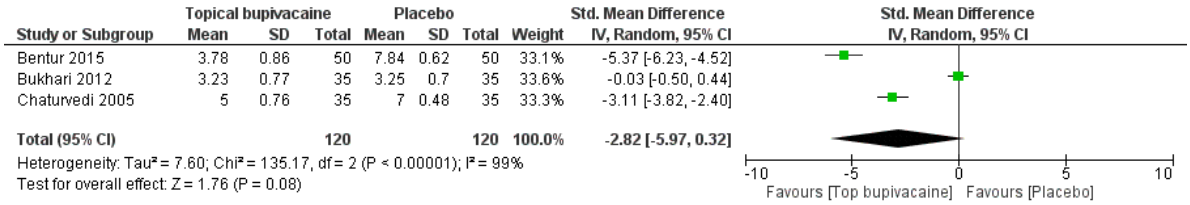


Fig. 4. Meta-analysis of pain scores 2-hours post-operation

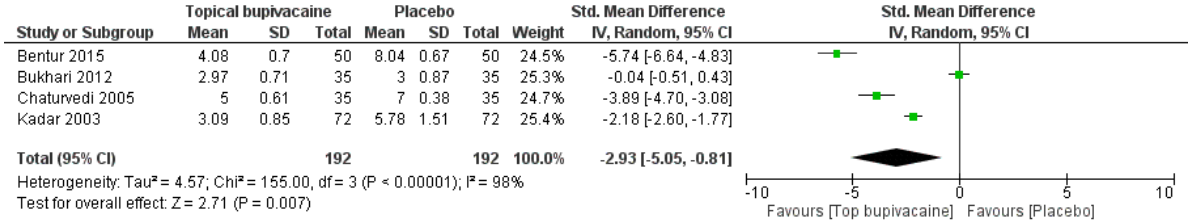


Fig. 5. Meta-analysis of pain scores 4-hours post-operation

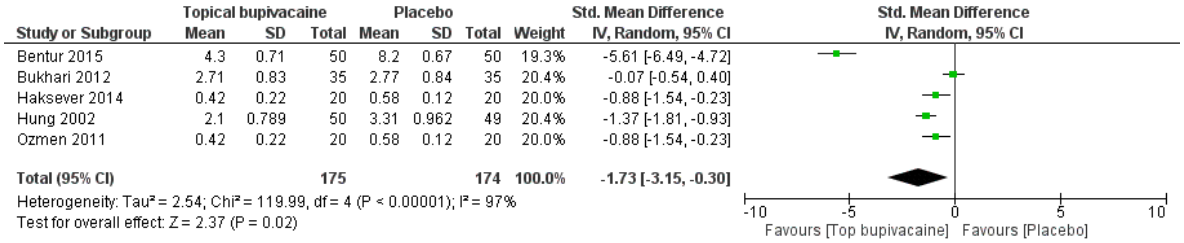


Fig. 6. Meta-analysis of pain scores 5 – 6 hours post-operation

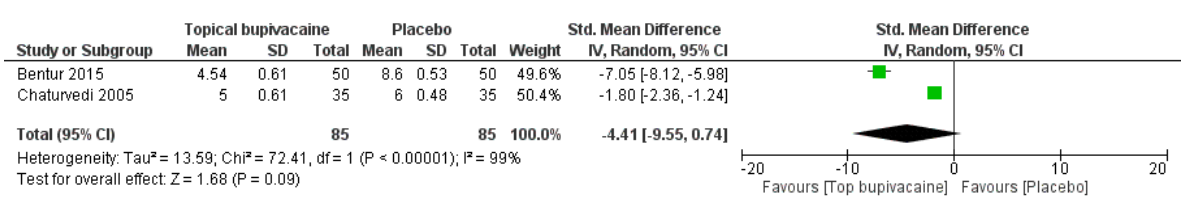


Fig. 7. Meta-analysis of pain scores 8-hours post-operation

Discussion

The results from this systematic review and meta-analysis indicate that topical bupivacaine produced a statistically significant reduction in pain score estimates at 1, 4- and 5-6-hours post-adenotonsillectomy when compared to placebo. The dose of bupivacaine was 0.5% for six studies, and 0.25% for one study. The included trials had noteworthy variation in the volume of bupivacaine used and differed in the duration of its application.

The equivocal results at 2-hours is suspected to be influenced by data from Bukhari et al. [27]. This was the only study whereby 0.25% bupivacaine (as opposed to 0.5%) was used. The lower concentration could potentially be the reason that pain scores from this study were not found to be significantly reduced when compared to placebo (and at 4-hours in the same study). Another likely reason for these results was that most of these patients had undergone combined adenotonsillectomies. The implication of this is greater tissue trauma as well as making it increasingly difficult for patients to successfully identify the source of their pain.

Although it is evident from current published literature that local anaesthetics do have a role in reducing post-tonsillectomy pain [6], the concern for safety with injected local anaesthetics remain. Studies have elucidated the complications associated with infiltration of local anaesthetic into the tonsillar fossa [13-16, 33]. This analysis reported no complications associated with use of topical bupivacaine and therefore highlights its safety profile in the management of pain post-adenotonsillectomy. The absence of complications is particularly important in resource constrained environments where there is a paucity of post-operative facilities. This is true for most developing countries. It is also advantageous in those environments where a fast-tracked surgery with enhanced recovery is feasible. It would allow patients to be discharged promptly with adequate analgesia. Duration of analgesia is also one cardinal factor in the choice of local anaesthetic to use.

Pain management was achieved with topical bupivacaine in the current study for periods of up to 6 hours postoperatively. Apart from variations in local anaesthetic, another confounding factor is surgical technique which can influence post-operative pain [34, 35]. The current study data appears to suggest a benefit (irrespective of surgical technique), of 0.5% topical bupivacaine application for a duration of 2-5 minutes. A noteworthy consideration is that none of the included studies had used bupivacaine with adrenaline. As a result, the effectiveness of the combination requires further evaluation before any recommendation or comparisons can be made. The studies did not report on additional post-operative analgesia required and this information could not be analysed.

There was significant heterogeneity in the analysis undertaken. This is possibly due to the considerable differences in population groups and study methods. Although all the included studies used validated pain scales, these differed in type and score ranges which may have influenced the statistical diversity. This was managed to some extent by using SMD which does limit this variation. Four studies allocated subjects to either intervention or control arms [25, 28-30]. Three studies used an ‘intra-individual’ design [13, 26, 27]. Even though this study design does reduce confounding variables, it presents several unique concerns. One being the possibility of cross contamination of the topical bupivacaine to the contralateral tonsillar fossa which can influence overall results. Another being that the youngest patient involved in these studies, which adopted this design, was three years old. The ability for younger patients to understand questions pertaining to pain localisation may have influenced the accuracy of the results.

The included studies comprised of both paediatric and adult patients. Although not evaluated in our meta-analysis due to the paucity of available detailed numerical data, there are differences in perceived pain between adults and children as well as that experienced between people of different genders. Children undergoing tonsillectomies tend to experience less post-operative pain within a week than adults [36]. Women are also at risk of experiencing more severe clinical pain with a greater predisposition to developing chronic pain than their male counterparts [37]. An appraisal of these differences within this surgical population is central for instituting personalised and best practice care guidelines.

Limitations

Despite the clinical impact of this meta-analysis, there were some limitations. Only literature in the English language was included. Included studies had relatively small sample sizes. This is in part due to poor reporting of data relating to this.

Conclusion

Topical bupivacaine was found to be effective and free of complications in reducing post-tonsillectomy pain scores. This method of administration is preferred as it avoids potentially serious complications that are associated with the infiltration technique. Bupivacaine is easily available and less costly. Larger future studies should clearly divide tonsillectomy from adenotonsillectomy, use consistent surgical and anaesthetic protocols, record the quantitative usage, or time to supplemental analgesia and use uniform validated pain scores.

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Conflict of interest

There are no conflicts of interest. (3826 words)

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Appendix 1

Search terms for electronic literature databases

PubMed Search

#	Keyword/s or Search term/s
1	Tonsil [Controlled vocabulary]
2	Tonsil* [Title/Abstract]
3	"Palatine tonsil" [Controlled vocabulary]
4	Adenoids [Controlled vocabulary]
5	Adenoid* [Title/Abstract]
6	Tonsillectomy [Controlled vocabulary]
7	Adenotonsillectom* [Title/Abstract]
8	Adeno-tonsillectom* [Title/Abstract]
9	"Post-tonsillectom*" [Title/Abstract]
10	"Post-adenoidectom*" [Title/Abstract]
11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12	Bupivacain* [Title/Abstract]
13	Bupivacaine [Controlled vocabulary]
14	Marcain* [Title/Abstract]
15	"1-Butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide" [Title/Abstract]
16	Carbostesin [Title/Abstract]
17	Buvacaina [Title/Abstract]
18	Dolanaest [Title/Abstract]
19	Sensorcaine [Title/Abstract]
20	"Local anesthe*" [Title/Abstract]

21	“Local anaesthe*” [Title/Abstract]
22	“Anesthetics, local” [Controlled vocabulary]
23	“Anesthesia, local” [Controlled vocabulary]
24	Anekain [Title/Abstract]
25	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
26	Topical* [Title/Abstract]
27	“Administration, topical” [Controlled vocabulary]
28	Spray* [Title/Abstract]
29	“Soaked swabs” [Title/Abstract]
30	#26 OR #27 OR #28 OR #29
31	#25 AND # 30
32	Placebo*[Title/Abstract]
33	Placebos [Controlled vocabulary]
34	“Placebo effect” [Controlled vocabulary]
35	“Saline solution” [Controlled vocabulary]
36	“Saline” [Title/Abstract]
37	#32 OR #33 #34 OR #35 OR #36
38	#30 AND #37
39	Pain* [Title/Abstract]
40	Pain [Controlled vocabulary]
41	“Acute pain” [Controlled vocabulary]
42	“Pain management” [Controlled vocabulary]
43	“Pain, postoperative” [Controlled vocabulary]
44	“Pain measurement” [Controlled vocabulary]

45	"Nociceptive pain" [Controlled vocabulary]
46	"Pain perception" [Controlled vocabulary]
47	"Pain, referred" [Controlled vocabulary]
48	"Pain, procedural" [Controlled vocabulary]
49	Discomfort [Title/Abstract]
50	Anesthesia and Analgesia [Controlled vocabulary]
51	Analgesia [Controlled vocabulary]
52	Analgesi* [Title/Abstract]
53	Insensitivit* [Title/Abstract]
54	Ache* [Title/Abstract]
55	#39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR 47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
56	#11 AND #31 AND #38 AND #55

Note: Concepts have been colour coded: Population (Blue), Intervention (Green), Comparison (Pink), Outcome (Yellow). Overall search results for all concepts combined: Red. In PubMed a combination of keywords/phrases (in Title/Abstract) and controlled vocabulary (MeSH) terms will be used to obtain the final search results for each concept.

Appendices

Appendix 1: Proposal and Annexures

Annexure 1: PRISMA Checklist

Annexure 2: Search strategies – electronic medical literature databases

Annexure 3: Datasheet

Annexure 4: PRISMA 2009 Flow Diagram

Appendix 2: Post graduate approval for protocol amendments

Appendix 3**:** Human research ethics committee clearance certificate

Appendix 4: Plagiarism/Turnitin report

Appendix 5: Journal guidelines to authors

Appendix 6: PRISMA Checklist

Appendix 1: Proposal and Annexures

The effectiveness of topical bupivacaine application versus placebo in managing pain in paediatric and adult adenotonsillectomy patients – a systematic review

Shainal Desai

348665

Shainal.desai@gmail.com

Supervisor:	Dr Sithandiwe Dingezweni
	MBChB, DA (SA), FCA (SA), Cert. of Critical Care (SA)
	Sdingezweni@ymail.com
	Department of Anaesthesiology, University of the Witwatersrand
Co-supervisor:	Dr Palesa Motshabi
	BSc, MBChB, DA (SA), FCA (SA), PhD
	Palesa.motshabi@wits.ac.za
	Department of Anaesthesiology, University of the Witwatersrand
Co-investigator:	Dr Yoshan Moodley
	BSc, BMedSc Hons, MmedSc, MPH, PhD
	Yoshan.moodley@wits.ac.za
	Department of Anaesthesiology, University of the Witwatersrand

1. Introduction

There is a high incidence of post-operative pain experienced by patients who have undergone adenotonsillectomies (1). This is a well-recognised factor contributing toward patient morbidity (1-3). Patients often struggle to eat, drink, talk or sleep as a result of pain. The majority of adenotonsillectomies are performed as elective day-case surgeries (4). This requires effective and safe pain management options which timeously allow patients to resume their daily activities. Local anaesthetics can be safely utilised to manage this pain (2). However, the best method of local anaesthetic administration has, up to date, been based on limited data. Bupivacaine is a long-acting local anaesthetic that is widely available, and commonly utilised, in the South African context. Infiltration of local anaesthetic has shown to be effective but also associated with complications (5-9). The inherent risk of infiltration is higher than topical application because the former requires the insertion of a needle and deposition of the drug into deeper tissue planes. This process can cause complications which are not seen with topical administration (2). In a resource constrained and overburdened setting, such as the South African public sector, the ideal method of administration of bupivacaine should ideally provide adequate analgesic effect and limit complications.

Tonsillectomy is a surgical procedure that involves the removal of lymphoid tissue called the palatine tonsils. These are located near the posterior aspect of the oral cavity (10). Adenoidectomy however, is the removal of lymphoid tissue, which is collectively known as adenoids. These are located behind the nasal passage and roof of the mouth (11). In some instances, the excision of both groups of lymphoid tissue are done simultaneously. These procedures can be carried out under local or general anaesthetic, with each method having some benefits and risks (12). Tonsillectomies performed under local anaesthesia is considered a safe alternative to general anaesthesia. Some benefits of this method include a reduction of post-operative analgesic consumption, cost and duration of surgery, while maintaining similar post-operative bleeding rates which does not appear to be dependent on anaesthetic type (12). According to Álvarez Palacios et al. (13), “Indications for tonsillectomy includes recurrent pharyngotonsillitis, chronic tonsillitis, peritonsillar abscess, haemorrhagic tonsillitis, suspicion of malignant diseases, and tonsillar hypertrophy causing obstructive sleep-disorder.” The two most common indications for carrying out an adenotonsillectomy in children is recurrent infection of the lymphoid tissue and obstructive sleep-disordered breathing (14). Obstructive sleep-disordered breathing encompasses a spectrum of sleep-

related breathing pathologies ranging from snoring to obstructive sleep apnoea. These conditions have shown to substantially affect patients' quality of life (14).

Tonsillectomies are now among the most commonly performed surgeries in the paediatric population with increased amounts seen in people over the age of 15 (15). In 1998, Canada had the lowest tonsillectomy rate reported in the literature, with a rate of 190 per 100 000 people under the age of 19 years. Northern Ireland had the highest reported rate of 880 per 100 000 in the same population (16). The number of adenotonsillectomies performed in the South African private healthcare sector is greater than that reported internationally (17). It was more than double the highest national tonsillectomy rate reported in Northern Ireland, with numbers of 1 888 per 100 000 people under the age of 19 years in 2012 and 1 755 per 100 000 in 2013 (17). These values most likely underestimate the actual rates within South Africa's private sector as they only used data provided by two medical aid schemes. These medical schemes comprised of only 37% of the private sector at the time (17). The authors postulate that this high rate is not due to an increased incidence of disease but rather variations in teaching and clinical practice, as well as societal and domestic factors (17). However, only 16% of South Africans can access private healthcare through medical aid schemes, and most adenotonsillectomies in South Africa are likely to be performed in the public sector. The adenotonsillectomy rate in the South African public sector is yet to be clearly defined. This is most likely due to the complexity of problems experienced in these over-burdened resource constrained facilities, inadequate record keeping and the lack of a surgical registry within the state healthcare sector (17). The higher rates in the South African private sector is in keeping with findings overseas. Countries with state mediated healthcare systems had lower tonsillectomy rates versus systems with private provisions and societal regulation or financing (18).

International investigations into regional variation of tonsillectomy rates have demonstrated that the relative proportion of children in the population, age, gender, health insurance status and parental education are all factors that influence tonsillectomy rates (19, 20). Despite medical advances and the popularity of the procedure, post-operative pain following adenotonsillectomy, is still a common complication.

Pain is a consequence of tissue damage, leading to the release of several inflammatory mediators such as substance P, histamine, bradykinin, and prostaglandins (21). These mediators act synergistically to generate and augment the transmission of nociceptive

impulses which are conducted by A delta fibres and C fibres to the spinal cord. They are then further relayed to the brain whereby the experience of pain is perceived (8). There are numerous factors that can influence pain post-adenotonsillectomy. One investigation presented an association between pre-operative chronic pain, younger age and female gender with more post-operative pain the day after tonsillectomy (22). This finding is in contrast to Alm et al. (23) that found no significant difference in patient reported pain-related outcome measures in patients of different ages or gender. They did however, find that post-operative pain was worse if the indication for the procedure was infective as opposed to obstructive in nature and if a hot surgical technique was used (23). Currently, two commonly used surgical techniques are the traditional cold steel and diathermy. There is not enough evidence to indicate that one method is superior to the other however, patients undergoing tonsillectomy using diathermy experience more pain but less bleeding (24, 25). In particular, the use of diathermy and the amount of energy used for electrocautery was the parameter that correlated the best with postoperative pain (26).

There are numerous complications that are associated with post-adenotonsillectomy pain. The most concerning of which is a delayed or poor oral intake with subsequent dehydration. Children, in particular, are at risk of additional complications such as sleep disruption, behavioural alterations and vomiting (27). There are also economic implications since these patients experience prolonged hospitalisations and require additional supplementary analgesia (3). Seshamani et al. (3), showed that the average cost of an uncomplicated tonsillectomy in an adult was US$ 3832. This increased to US$ 4708 if pain was experienced within the first 14 days post-surgery. The importance of adequate pain control therefore has several benefits.

One study had investigated the consequences of insufficient pain management in children post-tonsillectomy. Their results indicated that this population tend to experience considerable pain post-operatively, especially within the first 24 hours. During their telephonic interview with the parents of the 84 children who had undergone the procedure, it became evident that in most cases parents do not adhere to the prescribed medication (which was to be taken “as needed”). Parents were more inclined to under dose and in some instances use different medication completely (27). This inclination emphasises the importance of using modalities intra-operatively which have long acting benefits that extend into the post-operative phase. One method of achieving this goal is through the use of local anaesthetics.

The first operation that was performed using a local anaesthetic was in 1884. It involved an Austrian, Carl Koller, who had applied cocaine to the eye (28). Since then, advances have been made that have resulted in the production of numerous local anaesthetic agents with different pharmacokinetic and pharmacodynamic properties. The mechanism of action of local anaesthetics involves its ability to block the voltage-dependent sodium channels of axons. This inhibits the generation and propagation of impulses through a nerve (29). Other mechanisms of action of local anaesthetics include blocking of voltage-dependent calcium and potassium channels as well as G-protein-coupled receptors (GPCRs) (29, 30). Its effect on GPCRs is proposed to explain its antithrombotic and anti-inflammatory actions (30).

There are four local anaesthetic preparations that are included in the South African Acute Pain Guidelines (31). These are lignocaine, bupivacaine, levobupivacaine and ropivacaine. Lignocaine has a short duration of action and therefore has a limited role in managing post-operative pain (32). The availability of levobupivacaine and ropivacaine in the public sector is limited and provides the same quality of analgesia as bupivacaine when given in low doses (31).

Bupivacaine has a pKa of 8.1 resulting in a slow onset of action, with protein binding of 95% which results in its prolonged duration of action. The elimination half-life of bupivacaine is 120 minutes (33). Its versatility allows it to be used as either a topical or infiltrative agent. It is also effective for peripheral and neuraxial blocks. A unique characteristic of the drug is its ability to achieve a differential blockade depending on the concentration used. It is important to note that bupivacaine causes more severe cardiovascular and central nervous system toxic effects when compared to other local anaesthetics (28).

Studies have investigated the complications of utilising local anaesthetic, through infiltrative or topical application to the tonsillar fossae, for post-tonsillectomy pain (5, 8). There are several important risks associated with the infiltration of local anaesthetic into this area (8). It is a highly vascularised region and therefore accidental intravascular injection of the local anaesthetic can result in life threatening arrhythmias (8). Glossopharyngeal nerve block with inadvertent blockade of the vagus nerve can disrupt baroreceptor function resulting in tachycardia and hypertension (5). Significant upper airway obstruction is another potential concern once these nerves are concurrently blocked (5). Visual loss was described in one case report following the injection of penicillin, lignocaine and methylprednisone into the tonsillar fossae. The suggested mechanism was reported to be carotid artery vasospasm, however, this

was based on speculative evidence (7). Other case reports describe the development of cervical osteomyelitis and even bilateral vocal cord paralysis following infiltration (6, 9). Topical administration could potentially reduce the occurrence of these complications and still provide adequate analgesia (2).

Other classes of drugs are also used to manage adenotonsillectomy pain. Paracetamol, nonsteroidal anti-inflammatories (NSAIDs), opioids and N-methyl-D-aspartate (NMDA) receptor antagonists are some of the more commonly used agents. The use of such drugs is associated with serious potential complications and side effects. Preconceived notions that opioids provide better pain relief than NSAIDs, and that NSAIDs increase the risk of haemorrhage, are not supported by recent evidence (34). Opioid usage has however, been associated with constipation, respiratory depression, post-operative nausea and vomiting as well as addiction (35). Taking these factors into consideration, it is important that alternative methods of pain management are sought. This approach is supported by the 2019 American Academy of Otolaryngology Tonsillectomy Clinical Practice Guidelines which strongly recommend the use of acetaminophen (paracetomol) and ibuprofen but strongly recommend against the use of codeine (14).

Systematic reviews of the literature to date have limitations. There were no systematic reviews found that specifically address the role of topical bupivacaine in managing post-adenotonsillectomy pain. In 1999, the Cochrane Database of Systematic Reviews (36) analysed the use of peri-operative local anaesthesia for reducing pain following tonsillectomies. They concluded that there was not enough evidence at the time to support the use of local anaesthetic to control post-operative pain following tonsillectomies. This review included only six trials, of which five used infiltrative local anaesthetic and one used the topical agent benzydamine hydrochloride (36). Benzydamine is not a local anaesthetic but rather a topical NSAID with local anaesthetic properties (37). Limitations of this review were that it included studies with small sample sizes. A confounding factor in two of the studies was the use of long-acting opioids. This was thought to mask any effect that the local anaesthetic could have had on post-operative pain control. Studies that had adenoids removed concurrently were not included in the review due to the possibility of referred pain confounding results (36).

In 2008, Grainger et al. (2) conducted an updated systematic review and meta-analysis including 13 studies. Only two of the studies included reported use of topical local

anaesthetic, one of which used bupivacaine. They concluded that local anaesthetic results in a modest reduction in pain and advocated for topical over infiltrative method of administration, although this was based on information from only two studies (2).

Sun et al. (38) explored the role of peri-operative bupivacaine infiltration in relieving paediatric post-adenotonsillectomy pain (38). Their meta-analysis concluded that it is an effective method to manage pain in this setting. However, they acknowledged that the trials upon which their investigation was based, were small in size and of low quality. This could influence the reliability of their study and therefore they encouraged the need for further randomised controlled trials (RCT) (38).

A systematic review by Fedorowics et al. (10) investigated the use of topical agents in adenotonsillectomies (10). The drugs in the study comprised of lignocaine, benzydamine and hydrogen peroxide. They showed that lignocaine was more effective in managing pain than normal saline, although this effect was limited to day three post-operation. They recognised that the risk of bias was high in the selected studies and that there was poor reporting. As a result, a reliable conclusion could not be made (10).

A critical analysis of these reviews indicates that although local anaesthetics do have a role in managing post-adenotonsillectomy pain, the exact method of application has not been described based on reliable evidence. Given the above rates of this surgical procedure and the high incidence of post-operative pain, it is imperative that effective, yet safe methods of analgesia are sought. A collation and qualitative assessment of RCTs could provide evidence that would be useful in establishing whether topical local anaesthetic, in particular bupivacaine, is more effective than placebo. The implications of such results for peri-operative pain management could result in a method that is not only safe, effective and easy to administer, but also one that has financial benefits. This current study seeks to investigate the effectiveness of topical bupivacaine application in comparison to a placebo, in patients undergoing adenotonsillectomies, with the intention of providing high quality evidence for its use in a clinical setting.

2. Research Question

Is topical bupivacaine more effective in managing post-adenotonsillectomy pain than a placebo?

The concepts for the research question and the study are based upon the PICO framework:

- Population – paediatric and adult patients undergoing adenotonsillectomies

- Intervention – topical bupivacaine
- Comparison group – placebo/topical normal saline
- Outcome – post-operative pain.

3. Aim

The study seeks to investigate the effectiveness of topical bupivacaine in the management of postoperative pain in adenotonsillectomy patients compared to placebo.

4. Objectives

To describe the difference in effectiveness and outcomes of topical bupivacaine in managing post-adenotonsillectomy pain compared to placebo, with the use of a systematic review.

5. Methodology

5.1 General approach and study design

The general approach will be dictated by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for systematic reviews (Annexure 1) (39). This will include uploading the protocol to the International Prospective Register of Systematic Reviews (PROSPERO), appropriately designing, conducting, and reporting the review. An evidence-based approach will be used. It will be a quantitative systematic review of relevant randomised controlled studies with the potential for a meta-analysis. Systematic methodologies are the conventional method of identifying relevant literature for a collective review. As such, these studies provide the highest level of evidence along with randomized controlled trials.

5.1.1 Study population

The study population will include adults and children undergoing adenoidectomy or tonsillectomy or both.

5.1.2 Type of intervention

The topical application of bupivacaine to the surgical site.

5.1.3 Type of control

The topical application of a placebo/normal saline to the surgical site.

5.1.4 Types of outcome measured

Outcomes that will be sought:

- Information regarding a formal pain measuring tool (pain scale).
- Additional analgesic requirements in terms of time to first post-operative analgesic request and total amount of analgesic consumed (36).
- Complications associated with topical administration.

5.2 Sampling strategy

Abstracts of articles returned from the electronic medical literature database search will be screened for eligibility using the following inclusion/exclusion criteria. The inclusion criteria of eligible studies are as follows:

1) prospective, randomised controlled trials published until February 2020;
2) studies of patients who underwent either adenoidectomy or tonsillectomy, or both;
3) use of topical bupivacaine administration;
4) comparison of the effects of bupivacaine with placebo;
5) availability of detailed data.

The exclusion criteria are as follows:

1) single-arm studies;
2) in-vitro studies;
3) trials which did not report on any of the endpoints;
4) case reports;
5) retrospective studies;
6) duplicate study/publication;
7) manuscripts in non-English language;
8) studies in which a consistent anaesthetic protocol was not implemented.

Due to the clinical nature of the research, confounders would be present. However, randomization is the most optimal method of adjusting for confounders. By virtue that this is a systematic review and possible meta-analysis of RCTs, it is unlikely that confounding will play any role in the final results (40).

5.3 Data Analysis

Descriptive statistics will be used to present the characteristics of the eligible manuscripts. Should a meta-analysis be feasible, extracted data from included studies will be used to calculate the mean differences / standardised mean differences for continuous outcomes, odds ratios for binary outcomes, 95% confidence intervals and two-sided p-values for each outcome. A p-value < 0.05 will be considered statistically significant. The presence of

statistical heterogeneity of outcomes across trials will be assessed using the I^2 measure, and I^2>50% when p<0.10 indicates substantial heterogeneity. Trials with significant heterogeneity will be reported as standardised mean differences and those with insignificant heterogeneity as mean differences. Overall effects in studies with significant heterogeneity will be reported as random effects and those with insignificant heterogeneity as fixed effects. A meta-analysis will be performed with the assistance of a biostatistician using the RevMan 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) statistical software. These data analysis methods are conventionally used in meta-analysis (41). The following online calculator will be utilised to determine the power of the meta-analysis should it be feasible: https://mfr.osf.io/render?url=https://osf.io/juzfg/?direct%26mode=render%26action=download%26mode=render

5.4 Information sources

Three medical electronic databases (PubMed, Scopus and the Cochrane Library) will be used to search for relevant studies using a specific search strategy.

5.5 Search strategy and study selection

This search strategy was developed in accordance with the PICO framework and its detailed description for each database is attached as Annexure 2. The medical literature databases will be searched from the inception of the databases until the end of February 2020. The studies will then be screened for the inclusion and exclusion criteria. All studies that are eligible will be screened independently by a second reviewer. A third reviewer will cast the deciding vote on inclusion/exclusion of a study if there are any disagreements between the first two reviewers. In addition to the electronic database search, the reference lists of eligible articles will also be screened for relevant articles which might have been missed by the electronic database search.

The quality of the studies included will be determined using the Cochrane Risk of Bias Tools format. Version 2 of the tool for randomized trials is the recommended tool to assess the risk of bias in Cochrane Reviews (42). It is structured into a fixed set of domains of bias, focusing on different aspects of trial design, conduct, and reporting. Judgement can be 'Low' or 'High' risk of bias, or can express 'Some concerns'. The five domains include:

1) Bias due to randomisation (D1)
2) Bias due to deviations from intended intervention (D2)
3) Bias due to missing data (D3)

4) Bias due to outcome measurement (D4)
5) Bias due to selection of reported result (D5)

The above data will be placed in a Microsoft Excel spreadsheet (Table 1) and then Robvis (43), an online tool, will be used to create a summary of the assessment.

Disagreements of study quality will be resolved through discussion and a third reviewer consulted if a consensus is not reached.

Table 1. Cochrane Risk of Bias Data Sheet						
First author & year	D1	D2	D3	D4	D5	Overall

The following details will be extracted from the eligible articles:

- General study details: (a) authors, (b) year of publication, (c) country study was conducted in
- Participants: (a) sample size, (b) age groups, (c) male/female distribution, (d) operation – tonsil, adenoid or both removed, (e) surgical technique
- Intervention: (a) dosage, (b) length of time in follow-up.
- Control: (a) type (b) length of time in follow-up.
- Outcomes: (a) reduction in pain scores (using validated scales), (b) reduction in the demand for additional post-operative analgesia, (c) complications experienced.

These outcomes recorded for the first 24 hours post operatively will be taken into consideration. If consistent follow up exceeds this time frame in the literature, it too, will be included. This data will be extracted and placed on a data collection sheet (Annexure 3). All processes will be in accordance with the PRISMA flow diagram for systematic reviews (Annexure 4) (39). Data extraction and analysis will be carried out by the principal investigator.

5.6 Main study limitations

The review will only encompass findings from randomized controlled trials published as original research articles. Conference abstracts and other non-refereed reports will be excluded as it will be difficult to assess the quality of these reports and there is also a potential limitation in the amount of data which can be extracted. These sources are

potentially not peer-reviewed and additionally in the case of conference proceedings, there is usually insufficient information in the abstract to include this in an analysis.

5.7 Study ethical approval

This is a systematic review of the literature (data in the public domain), and there will be no direct patient involvement or potential harm to patients. Therefore, the investigator will apply to the University's Ethics Committee, which is registered with the National Health Research Ethics Council (NHREC) of the Department of Health, for a waiver of ethics or expedited minimally invasive research application.

6. Timeline

This is an estimated projection of intermediary steps and completion of research:

Activity	09	10	11	12	01	02	03	04	05	06	07	08
	2019				2020							
Proposal preparation												
Literature review												
Proposal submission												
Corrections to proposal												
Ethics approval/ waiver												
Postgraduate approval												
Data collection												
Data analysis												
Draft article												
Submission												

7. Support and financial plan

There is no review funder or sponsor. The Department of Anaesthesiology will bear the cost of paper and printing. Estimated budget that is required for printing purposes:

Item	Price per page	Number of pages	Copies	Total
Proposal	1	25	10	R 250
Ethics	1	5	2	R 10
Post graduate form	1	2	6	R 12
Complete report	1	100	4	R 400
Grand total				R 672

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Annexure 1: PRISMA Checklist (39)

Section/topic	#	Checklist item
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	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication

across studies		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 (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., healthcare 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.

Annexure 2: Search strategies – electronic medical literature databases

PubMed Search

#	Keyword/s or Search term/s
1	Tonsil [Controlled vocabulary]
2	Tonsil* [Title/Abstract]
3	"Palatine tonsil" [Controlled vocabulary]
4	Adenoids [Controlled vocabulary]
5	Adenoid* [Title/Abstract]
6	Tonsillectomy [Controlled vocabulary]
7	Adenotonsillectom* [Title/Abstract]
8	Adeno-tonsillectom* [Title/Abstract]
9	"Post-tonsillectom*" [Title/Abstract]
10	"Post-adenoidectom*" [Title/Abstract]
11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12	Bupivacain* [Title/Abstract]
13	Bupivacaine [Controlled vocabulary]
14	Marcain* [Title/Abstract]
15	"1-Butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide" [Title/Abstract]
16	Carbostesin [Title/Abstract]
17	Buvacaina [Title/Abstract]
18	Dolanaest [Title/Abstract]
19	Sensorcaine [Title/Abstract]
20	"Local anesthe*" [Title/Abstract]
21	"Local anaesthe*" [Title/Abstract]
22	"Anesthetics, local" [Controlled vocabulary]
23	"Anesthesia, local" [Controlled vocabulary]

24	Anekain [Title/Abstract]
25	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
26	Topical* [Title/Abstract]
27	"Administration, topical" [Controlled vocabulary]
28	Spray* [Title/Abstract]
29	"Soaked swabs" [Title/Abstract]
30	#26 OR #27 OR #28 OR #29
31	#25 AND # 30
32	Placebo*[Title/Abstract]
33	Placebos [Controlled vocabulary]
34	"Placebo effect" [Controlled vocabulary]
35	"Saline solution" [Controlled vocabulary]
36	"Saline" [Title/Abstract]
37	#32 OR #33 #34 OR #35 OR #36
38	#30 AND #37
39	Pain* [Title/Abstract]
40	Pain [Controlled vocabulary]
41	"Acute pain" [Controlled vocabulary]
42	"Pain management" [Controlled vocabulary]
43	"Pain, postoperative" [Controlled vocabulary]
44	"Pain measurement" [Controlled vocabulary]
45	"Nociceptive pain" [Controlled vocabulary]
46	"Pain perception" [Controlled vocabulary]
47	"Pain, referred" [Controlled vocabulary]

48	"Pain, procedural" [Controlled vocabulary]
49	Discomfort [Title/Abstract]
50	Anesthesia and Analgesia [Controlled vocabulary]
51	Analgesia [Controlled vocabulary]
52	Analgesi* [Title/Abstract]
53	Insensitivit* [Title/Abstract]
54	Ache* [Title/Abstract]
55	#39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR 47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
56	#11 AND #31 AND #38 AND #55

Note: Concepts have been colour coded: Population (Blue), Intervention (Green), Comparison (Pink), Outcome (Yellow). Overall search results for all concepts combined: Red. In PubMed a combination of keywords/phrases (in Title/Abstract) and controlled vocabulary (MeSH) terms will be used to obtain the final search results for each concept.

SCOPUS Search

#	**Keyword/s or Search term/s**
1	Tonsil* [Title/Abstract/Keyword]
2	Adenoid* [Title/Abstract/Keyword]
3	Adenotonsillectom* [Title/Abstract/Keyword]
4	"Adeno-tonsillectom*" [Title/Abstract/Keyword]
5	"Post-tonsillectom*" [Title/Abstract/Keyword]
6	"Post-adenoidectom*" [Title/Abstract/Keyword]
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	Bupivacain* [Title/Abstract/Keyword]
9	Marcain* [Title/Abstract/Keyword]
10	"1-Butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide"

	[Title/Abstract/Keyword]
11	Carbostesin [Title/Abstract/Keyword]
12	Buvacaina [Title/Abstract/Keyword]
13	Dolanaest [Title/Abstract/Keyword]
14	Sensorcaine [Title/Abstract/Keyword]
15	Anekain [Title/Abstract/Keyword]
16	“Local anesthetic” [Title/Abstract/Keyword]
17	“Local anaesthetic” [Title/Abstract/Keyword]
18	#8 OR #9 OR 10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
19	Topical* [Title/Abstract/Keyword]
20	Spray* [Title/Abstract/Keyword]
21	“Soaked swabs” [Title/Abstract/Keyword]
22	#19 OR #20 OR #21 OR #22
23	#18 AND # 22
24	Placebo* [Title/Abstract/Keyword]
25	Saline [Title/Abstract/Keyword]
26	#24 OR #25
27	#22 AND #26
28	Pain* [Title/Abstract/Keyword]
29	Discomfort* [Title/Abstract/Keyword]
30	Analgesi* [Title/Abstract/Keyword]
31	Insensitivit* [Title/Abstract/Keyword]
32	Ache* [Title/Abstract/Keyword]
33	#28 OR #29 OR #30 OR #31 OR #32
34	#7 AND #23 AND #27 AND #33

Note: Concepts have been colour coded: Population (Blue), Intervention (Green), Comparison (Pink), Outcome (Yellow). Overall search results for all concepts combined: Red. In Scopus only phrases (Title/Abstract/Keywords) will be searched as the database does not have a controlled vocabulary.

Cochrane Search

#	**Keyword/s or Search term/s**
1	Tonsil* [Title/Abstract/Keyword]
2	Adenoid* [Title/Abstract/Keyword]
3	Adenotonsillectom* [Title/Abstract/Keyword]
4	"Adeno-tonsillectom*" [Title/Abstract/Keyword]
5	"Post-tonsillectom*" [Title/Abstract/Keyword]
6	"Post-adenoidectom*" [Title/Abstract/Keyword]
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	Bupivacain* [Title/Abstract/Keyword]
9	Marcain* [Title/Abstract/Keyword]
10	"1 Butyl N 2,6 dimethylphenyl 2 piperidinecarboxamide" [Title/Abstract/Keyword]
11	Carbostesin [Title/Abstract/Keyword]
12	Buvacaina [Title/Abstract/Keyword]
13	Dolanaest [Title/Abstract/Keyword]
14	Sensorcaine [Title/Abstract/Keyword]
15	Anekain [Title/Abstract/Keyword]
16	"Local anesthetic" [Title/Abstract/Keyword]
17	"Local anaesthetic" [Title/Abstract/Keyword]
18	#8 OR #9 OR 10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
19	Topical* [Title/Abstract/Keyword]
20	Spray* [Title/Abstract/Keyword]
21	"Soaked swabs" [Title/Abstract/Keyword]
22	#19 OR #20 OR #21 OR #22

23	#18 AND # 22
24	Placebo* [Title/Abstract/Keyword]
25	Saline [Title/Abstract/Keyword]
26	#24 OR #25
27	#22 AND #26
28	Pain* [Title/Abstract/Keyword]
29	Discomfort* [Title/Abstract/Keyword]
30	Analgesi* [Title/Abstract/Keyword]
31	Insensitivit* [Title/Abstract/Keyword]
32	Ache* [Title/Abstract/Keyword]
33	#28 OR #29 OR #30 OR #31 OR #32
34	#7 AND #23 AND #27 AND #33

Note: Concepts have been colour coded: Population (Blue), Intervention (Green), Comparison (Pink), Outcome (Yellow). Overall search results for all concepts combined: Red. In Cochrane only phrases (Title/Abstract/Keywords) will be searched as the database does not have a controlled vocabulary.

Annexure 3: Datasheet

Study title:	
Date:	**Time:**

General study details		
Authors	**Year of publication**	**Country study was conducted in**

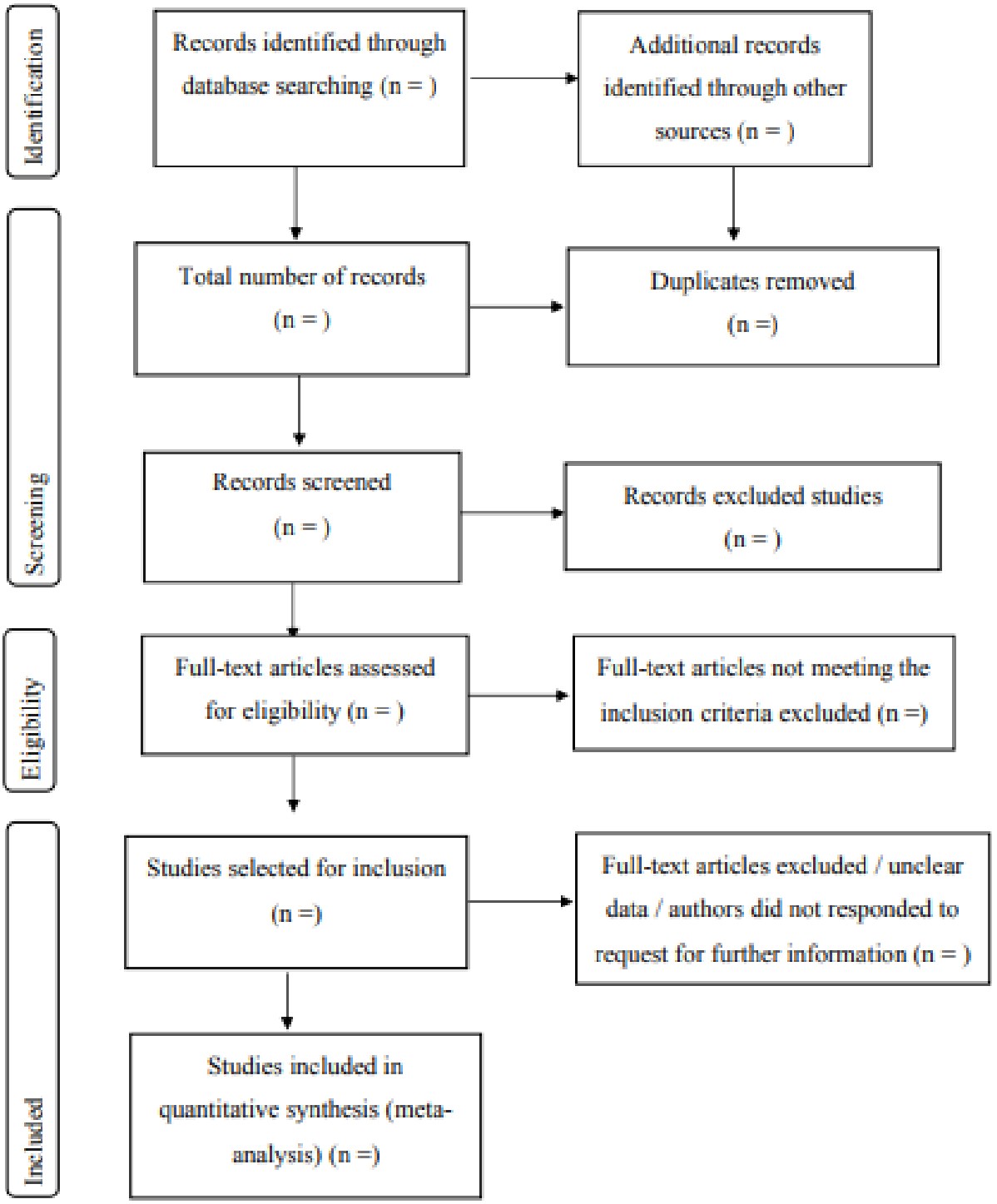
Participants				
Sample size	**Age groups**	**Male/female distribution**	**Operation**	**Surgical technique**

Intervention	
Dosage	**Length of time in follow-up**

Control	
Dosage	**Length of time in follow-up**

Outcomes		
Reduction in pain scores	**Reduction in the demand for additional post-operative analgesia**	**Complications experienced**

Annexure 4: PRISMA 2009 Flow Diagram (39)



Appendix 2: Post graduate approval for protocol amendments

WITS UNIVERSITY

DEPARTMENT OF ANAESTHESIOLOGY
UNIVERSITY OF THE WITWATERSRAND,
JOHANNESBURG
Tel.(011)933-9334/5 / Fax (011)933-1843

FACULTY OF HEALTH SCIENCES

6 March 2020

To whom it may concern
Office of the Faculty Registrar: Clinical Disciplines
Faculty of Health Sciences

RE: RESEARCH CORRECTIONS – MMed Dr Shainal Desai (348665)

This is to acknowledge that Dr Christopher Anamourlis and I have read Dr Shainal Desai's corrections as proposed at the Protocol Assessor's Meeting on 16 October 2019 for his MMed research proposal titled:

"The effectiveness of topical bupivacaine application versus placebo in managing pain in paediatric and adult adenotonsillectomy patients – a systematic review"

We were both part of the panel at that meeting and the request was made for me to review it. A second opinion was obtained from Dr Christopher Anamourlis. We are both satisfied that he has appropriately addressed corrections suggested by the postgraduate committee, and can now submit his revised proposal with all the required documents.

With kind regards.
Yours sincerely.

Dr Maria Fourtounas
Specialist anaesthetist
Department of Anaesthesia
University of the Witwatersrand
Email: maria.fourtounas@gmail.com / maria.fourtounas@wits.ac.za
Cell: 0827751345
Work: 011 933 9334

Appendix 3: Human research ethics committee clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Dr S Desai
School: Clinical Medicine
Department: Anaesthesia
Medical School
University
E-mail: shainal.desai@gmail.com

CC: Supervisor: Dr S Dingezweni <sdingezweni@ymail.com>
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 04/08/2020

REF: *R14/49*

PROTOCOL NO: W-CBP-200804-01 (This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)

PROJECT TITLE: *The effectiveness of topical bupivacaine application versus placebo in managing pain in paediatric and adult adenotonsillectomy patients - a systematic review*

Please find attached the Ethics Waiver Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/ClearScanWaiver.wps

Appendix 4: Plagiarism/ Turnitin report

348665:MMed_Final_Article_-_348665Desai.pdf

ORIGINALITY REPORT

14%	10%	11%	4%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	perioperativemedicinejournal.biomedcentral.com Internet Source	1%
2	Ozmen, S., O. A. Ozmen, and F. Kasapo lu. "Effects of Levobupivacaine versus Bupivacaine Infiltration on Postoperative Analgesia in Pediatric Tonsillectomy Patients: A Randomized, Double-Blind, Placebo-Controlled Study", Annals of Otology Rhinology & Laryngology, 2011. Publication	1%
3	Submitted to University of Leeds Student Paper	1%
4	J. Grainger. "Local anaesthetic for post-tonsillectomy pain: a systematic review and meta-analysis", Clinical Otolaryngology, 10/2008 Publication	1%
5	www.annfammed.org Internet Source	1%

Appendix 5: South African Medical Journal (SAMJ) guidelines to authors

Author Guidelines

The *SAMJ* has launched a new submission and tracking system. Authors will be required to register a profile on the Editorial Manager platform in order to submit a manuscript.

To submit a manuscript, please proceed to the *SAMJ* Editorial Manager website:

www.editorialmanager.com/samj

To access and submit an article already in production, please see the guidelines here.

Author Guidelines

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

SAMJ policies

- Types of articles considered by the SAMJ
- Article Processing Charges
- Authorship
- Conflict of interest
- Research ethics committee approval
- Clinical trials
- Protection of patient's rights to privacy
- Copyright notice
- Privacy statement
- Ethnic classification
- CPD

Manuscript preparation

- Preparing an article for anonymous review
- General article format/layout
- Preparation notes by article type
- Illustrations
- Tables
- References

From submission to acceptance

- Submission and peer-review
- Production process
- Changing contact details or authorship

Publication

- Online versus print
- Errata and retractions
- Indexing

SAMJ Policies

Type of articles considered by the SAMJ

The *SAMJ* will no longer limit the articles accepted to those that have 'general medical content', but is intending to capture the spectrum of medical and health sciences, grouped by relevance to the country's burdens of disease. This content will include research in the social sciences and economics that is relevant to the medical issues around our burden of disease. Please see 'A new vision for the *SAMJ* – and a call for papers' for a full discussion of the new directions for the *SAMJ*.

We accept the following types of articles:

- Research
- Reviews
- Clinical trials
- Editorials
- In Practice (Previously Forum incl. Case Reports)
- Correspondence
- Obituaries
- Book reviews
- Ad hoc supplements e.g. guidelines, conference/congress abstracts, Festschrifts*

The following articles are by invitation only:

- Guest editorial
- Continuing Medical Education (CME)

*Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Publication Fees

All articles published in the *South African Medical Journa*l are open access and freely available online upon publication. This is made possible by applying a business model to offset the costs of peer review management, copyediting, design and production, by charging a publication fee of R5 731.95 (ex vat) for each research article published. The charge applies only to Research articles submitted after 1 March 2017. The publication fee is standard and does not vary based on length, colour, figures, or other elements.

When submitting a Research article to the *SAMJ*, the submitting author must agree to pay the publication fee should the article be accepted for publication. The publication fee is payable when your manuscript is editorially accepted and before production commences for publication. The submitting author will be notified that payment is due and given details on the available methods of payment. Prompt payment is advised; the article will not enter into production until payment is received.
Queries can be directed to claudian@hmpg.co.za.

Please refer to the section on 'Sponsored Supplements' regarding the publication of supplements, where a charge is applicable. Queries can be directed to dianes@hmpg.co.za or claudian@hmpg.co.za

Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structures to ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchers have been adhered to.

Clinical trials

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an

intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. All clinical trial reports must also contain a data sharing statement as per the recommendations of the ICMJE. Statements are to indicate:

- whether individual deidentified participant data will be shared;
- what data in particular will be shared; whether additional, related documents will be available;
- when the data will become available and for how long; by what access criteria data will be shared.

Please see the ICJME announcement for further details and illustrative examples of data sharing statements: ICMJE Data Sharing Statements for Clinical Trials.

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The SAMJ therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrolment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Patient Consent

Information that would enable identification of individual patients should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the *SAMJ*.

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Material submitted for publication in the *SAMJ* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement. All research already published as 'Conference proceedings' needs to be substantially re-written, with a new title, a new abstract and new and important results to back up any study before it will be considered for a new publication. The *SAMJ* does not hold itself responsible for statements made by the authors.

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Privacy statement

The *SAMJ* is committed to protecting the privacy of its website and submission system users. The names, personal particulars and email addresses entered in the website or submission system will not be made available to third parties without the user's permission or due process. By registering to use the website or submission system, users consent to receive communication from the *SAMJ* or its publisher SAMA on matters relating to the journal or associated publications. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note that is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Continuing Professional Development (CPD)

SAMJ is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *SAMJ* also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state ‘none’.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

- Research
- Editorials
- CME
- In Practice and Case reports
- Reviews
- Clinical trials
- Correspondence
- Obituaries
- Book reviews
- Guidelines

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text.

Structured abstract

- This should be 250-400 words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

CME (by invite only)

CME is intended to provide readers with practical, up-to-date information on medical and related matters. It is aimed at those who are not specialists in the field.

From January 2016, all CME articles will be printed in full in the *SAMJ*. Please try to adhere strictly to the guidelines on word count as we have a page limit for the print issue of the *SAMJ*. We reserve the right to place some tables and reference lists online if this is necessary for space.

In practice, this means that each CME topic usually covers two issues of the print issue of the *SAMJ*.

The guest editor, in consultation with the editor, is responsible for convening a team of authors, deciding on the subjects to be covered and for reviewing the manuscripts submitted. The suggestion is for 4 - 5 articles, although there is some room for flexibility contingent on discussions with the editor.

For queries about these guidelines please feel free to contact the CME editor, Dr Bridget Farham, by email (ugqirha@iafrica.com) or telephone (+27 (0)82 452 2860)

Review process

The guest editor reviews the articles and returns them to the CME editor for review and final approval.

Guest editorials

Guideline word limit: 1 000 words

- Include the guest editor's personal details (qualifications, positions, affiliation, e-mail address, and a short personal profile (50words)).
- If possible, include a photograph of the author(s) at high enough resolution for print. It is preferable to provide two guest editorials, one for each issue, so that the content of the articles in each issue is covered.

Articles

Guideline word limit: 2 000 - 3 000 words

- Each article requires an abstract of ±200 words.
- The editor reserves the right to shorten articles but will send a substantially shortened article back for author approval.

Personal details

Please supply: Your qualifications, position and affiliations and MP number (used for CPD points); Address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

In Practice

Guideline word limit: 2 000 - 3 000words

This section includes articles that would previously have been accepted into the Forum section, and case reports.

In practice articles are those that draw attention to specific issues of clinical, economic or political interest regarding medicine and healthcare in southern Africa. They are assigned to a topic:

- Case report
- Clinical practice
- Clinical alert
- Issues in medicine
- Issues in public health
- Healthcare delivery
- Medicine and the environment
- Medicine and the law
- Cochrane corner

An In Practice article should follow the following format – sub-headings are not necessary, but may be used for clarity:

- Author affiliations and qualifications: to be the same as for Research. Provide all authors' names and initials, qualifications and full affiliations, and corresponding author.
- Short abstract: does not need to be structured, but should capture the essential features of the article
- Introduction: the reason for the article and the issue being addressed
- Recent research, discussion, local policy around the issue – include your own research where appropriate
- All statements should be referenced and, if opinion only, this should be stated
- Discussion: how this article adds to the discussion around a particular topic
- If a clinical practice or policy point is at issue, this needs to be emphasised, using a box with highlights if appropriate.

Essentially In practice is an opportunity for a more discursive approach to topics of clinical, economic or political importance in southern African health systems. It is not an opportunity to put forward unsubstantiated opinions!

Case reports

The *SAMJ* has recently started to accept case reports. The cases must come from Africa, preferably southern Africa unless the condition is common to all African countries, and must be either a completely new description of a clinical condition or result (use Google!) or a case that highlights important practice or management issues.

Please use the following format for case reports:

- Title of case: do not include the words 'a case report' in the title
- Summary/abstract: up to 150 words summarising the case presentation and outcome
- Background: why is this case important and why did you write it up?
- Case presentation: presenting features, medical, social, family history as appropriate

- Case management: should be according to best practice, and if not, please explain why
- Investigations, if relevant: save space by simply saying 'normal' if, for example, renal function was completely normal, rather than listing normal results, highlight the abnormal – or indeed the normal if this is clinically significant
- Differential diagnosis, if relevant
- Treatment, if relevant
- Outcome and follow-up
- Discussion – a VERY BRIEF review of similar published cases
- Teaching points: 3 - 5 bullet points
- References: as per the *SAMJ* house style
- Tables and figures: keep to a minimum. Use clinical images where relevant – we need hi-res versions for print, and identifiable persons must have a consent form
- Patient consent: please include a statement about patient consent to a written case report. This should be uploaded as a supplementary file.

Clinical trials

Guideline word limit: 4000 words

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register.
The *SAMJ* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Review articles

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners.

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.

- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 500 words

Letters to the editor should relate either to a paper or article published by the SAMJ or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address

Book reviews

Guideline word limit: 400 words

Should be about 400 words and must be accompanied by the publication details of the book. Provide a hi-res image of the cover if possible (with permission from the copyright holder).

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Guidelines

Guidelines should always be discussed with the Editor prior to submission.

Because of the intensive review process required to ensure Guidelines are independent, evidence-based and free from commercial bias, they are usually published as a supplement to the *SAMJ*, the costs of which must be covered by sponsorship, advertising or payment by the guideline authors/association. We will provide a quote based on the expected length of the guideline and whether it is to appear online only, or in print, which must be accepted by the body putting the guidelines together before submitting the work to the SAMJ.

The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

All guidelines should include a clear, transparent statement about all sources of funding and an explicit, clear statement of conflicts of interest of any of the participants in the guidelines about industry funding for lectures, research, conference participation etc.

All guidelines should be structured according to Agree II.

Please access this website before putting the guidelines together, download the Agree 11 instrument and use this to put the guidelines together.

All submitted guidelines will be sent to the local Agree II appraisal committee for review and must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed.

A structured abstract not exceeding 400 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2.etc.) and summarised in a Table of Contents.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make ‘new rows’:

Rather:
Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:
Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:
Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
    - On the Crossref homepage, paste the article title into the 'Metadata search' box.
    - Look for the correct, matching article in the list of results.
    - Click Actions > Cite
    - Alongside 'url =' copy the URL between { }.
    - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.

- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references

• Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

• Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

• Acts:

South Africa. National Health Act No. 61 of 2003.

• Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

• Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

• Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

• Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) would indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.

- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

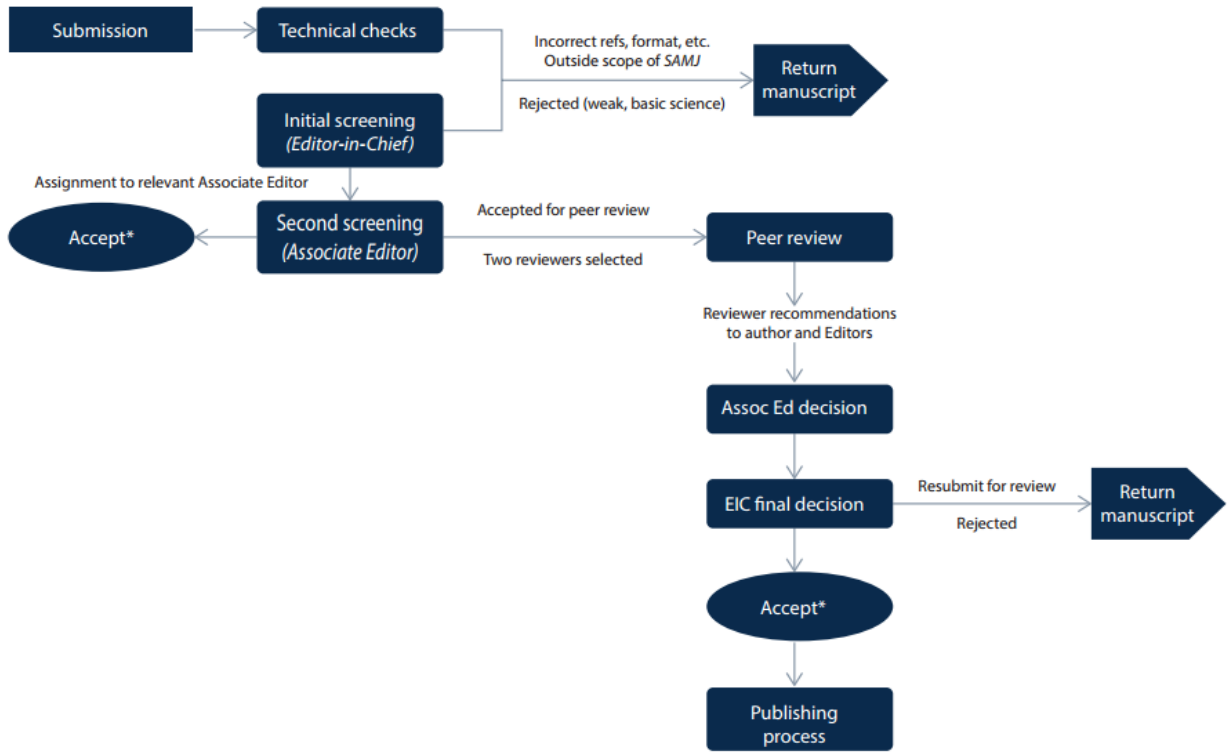
From submission to acceptance

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the SAMJ requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
    - Anonymous manuscript (unless otherwise stated)
    - Manuscript
    - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
- Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer-review process



*Manuscripts accepted at this point are limited to Editorials, Correspondence, Obituaries, Book reviews, Abstracts, CME
**Some minor revisions may be requested

Production process

Please note that there is a 6-month waiting time for publication, once an article has been sent to the production team.

The following process will follow:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.
3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
5. The CE will finalise the article and then it will be typeset.
6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.
7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Publication

Online v. print

The *SAMJ* is an online journal. The online version of the journal is the one that has the widest circulation, is indexed by bibliographic databases including PubMed and SciELO, and is accessible in academic libraries. A printed edition , containing material selected by the Editor is also published each month and distributed to the membership of the South African Medical Association.

Online

- The full text of all accepted articles is published in full online, open access.
- Citation information of each article is based on its online publication.
- You may want to make use of the advantages of online publication e.g. specify web links to other sources, images, data or even a short video.

Print

- Not all articles will be selected for print.
- An article may be selected for print in a different month from that in which it was published online.
- Research articles will appear *in abstract form only*, if selected for a print edition.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@hmpg.co.za,including the following details:

- Journal, volume and issue in which published
- Article title and authors
- Description of error and details of where it appears in the published article
- Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish anerratum in the next issue. The correction will be indexed, as PubMed has a function for linking errata back to the original article. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

Retractions

Retraction of an article is the prerogative of either the original authors or the editorial team of SAMA. Should you wish to withdraw your article before publication, we need a signed statement from all the authors.

Should you wish to retract your published article, all authors have to agree in writing before publication of the retraction.

Send an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue to which article was submitted/in which article was published
- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

Indexing

The *SAMJ* has an impact factor of 1.5.

Published articles are covered by the following major indexing services. As such articles published in the *SAMJ* are immediately available to all users of these databases, guaranteed a global and African audience:

- Index Medicus (Medline/PubMed)
- ExcerptaMedica (EMBASE)

- Biological Abstracts (BIOSIS)
- Science Citation Index (SciSearch)
- Current Contents/Clinical Medicine
- Scopus
- AIM
- AJOL
- Crossref
- Sabinet
- Scielo

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Appendix 6: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
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.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4 - 5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
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.	5
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.	5
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.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5; 19 - 21
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).	5
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.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
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.	6

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
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.	6
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).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
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.	7
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.	8
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).	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11 - 13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11 - 13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
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., healthcare providers, users, and policy makers).	14 - 15
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).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
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.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.