Assessment of Pain Management in Anaesthesia

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Abstract

Pharmacotherapy within anaesthesia includes pain relief with an aim to ensure patient comfort through adequate analgesia and sedation. To control acute pain within intra-operative and post-operative scenarios, paracetamol, opiates, and NSAIDS are used. Selective COX-2 inhibitors celecoxib, parecoxib and the selective α2-AR agonist dexmedetomidine are currently not available on the local hospital formulary for use within the Anaesthesia department.

This study aimed to gather evidence regarding indications and advantages of celecoxib, parecoxib and dexmedetomidine, to assess the value of these drugs for inclusion in the local formulary for use in pain management, and to identify local clinicians' perspective regarding these drugs.

Scientific evidence was gathered from Summary of Product Characteristics (SPCs) and through a literature review. Feedback from pain specialists and anaesthetists (N=18) within the Department of Anaesthesia, Mater Dei Hospital, was sought via an online questionnaire. Both celecoxib and parecoxib carry a marketing authorisation for the relief of acute postoperative pain. They have similar pharmacological properties but exhibit lower GI side effects relative to other NSAIDs. Celecoxib is highly COX-2 specific but has reduced aqueous solubility, limiting its dosage options. Parecoxib, the water-soluble prodrug of valdecoxib, is the only injectable COX-2. No evidence indicates superior degrees of pain relief between the two, but parecoxib offers advantages in the immediate post-operative scenario, when oral administration is not possible[1]. Dexmedetomidine serves as a sedative

[1] Gajraj NM. COX-2 inhibitors celecoxib and parecoxib: valuable options for postoperative pain management. Current topics in medicinal chemistry. 2007 Feb 1;7(3):235-49.

and analgesic agent, it is indicated in ITU patients and poses less risk of causing respiratory depression, delirium and agitation compared to other opioids.

Local anaesthetists feel limited in prescribing with the absence of these drugs. They tallied with evidence from literature that these are valuable agents to be included within the local formulary because of their advantageous dosage forms and safety profiles. From the three agents, dexmedetomidine was given highest priority for introduction.

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List of Abbreviations

- α2-AR – Alpha-2-adrenergic receptor
- Ach – Acetylcholine
- ADR – Adverse Drug Reaction
- BNF – British National Formulary
- CCU – Critical Care Unit
- COX – Cyclo-oxygenase enzyme
- EBSCO – Cochrane Database of Systematic Reviews
- EMC – Electronic Medicines Compendium
- GI – Gastrointestinal
- IHD – Ischaemic Heart Disease
- IM – intramuscular
- ITU – Intensive Therapy Unit
- IV – Intravenous
- IVI – Intravenous Infusion
- MMA – Malta Medicines Authority
- NCBI – National Center for Biotechnology Information
- NMBA – Neuromuscular Blocking Agents
- NSAIDs – Non-Steroidal Anti-Inflammatory Drugs
- SPC – Summary of Product Characteristics

Chapter 1

Introduction

1.1 ITU Setting

The Intensive Therapy Unit (ITU), also referred to as Critical Care Unit (CCU), is a highly specialised department aimed at providing individualised care for patients suffering from life-threatening conditions.[1] Critically-ill patients require constant monitoring and treatment for serious illnesses and major injuries (Phelan, 2018). Moreover, the ITU also provides high-dependency care for patients requiring less monitoring, as with following a major surgery, for those suffering from any other underlying medical conditions.[2]

Processes that occur within the intensive therapy unit entail highly specific, complex care that is provided to a heterogeneous population (Moreno and Metnitz, 2008). Most admissions in ITU are unplanned as the majority of cases deal with emergency situations such as devastating car accidents. However, some planned admissions do occur. An example of which includes admission following a major surgery. A highly professional multidisciplinary team is necessary to provide such specialised care since this is the most renowned high-risk area within the healthcare setting. Patients within this ward require the need to be

[1] Brighton and Sussex University Hospitals NHS Trust. The Intensive care unit: Information for relatives of relatives, patients and carers [Internet]. United Kingdom: 2018 [cited 2021 August 12]. Available from URL: https://www.bsuh.nhs.uk/wp-content/uploads/sites/5/2016/09/The-Intensive-Care-Unit.pdf

[2] National Health Service (NHS). Intensive Care [Internet]. United Kingdom: NHS; 2016 [cited 2021August 12]. Available from URL: https://www.nhs.uk/conditions/Intensive-care/

continuously monitored and are thus always accompanied by a specialised ITU Charge nurse. Generally, one nurse is responsible for one patient at a time.[3]

The primary aim of patient therapy, within this environment especially, is to be successful in providing the best possible efficacious treatment of the highest quality, in the shortest amount of time resulting in the least possible duration of stay (Moreno and Metnitz, 2008). In this way, besides deducting the financial strains (which are no doubt higher than in any other ward due to the inevitable use of medical equipment such as ventilators, dialysers as well as other devices used to monitor the patient's conditions), it also helps in reducing the risk of obtaining nosocomial infections. To achieve this, the use of evidence-based medicine is required.[3] This will aid in sustaining and restoring the health condition of these critically ill patients, to their more productive lives (Narayanan et al, 2016).

Pharmacotherapy is thus mainly related to pain relief and patient comfort so as to meet the primarily goals of patient therapy; to provide adequate analgesia and sedation (Murray et al, 2008). Within the ITU setting however, this can be challenging to achieve due to any underlying conditions the patient suffers from in addition to the critical illness. The right medication choice is imperative not only to improve the state of the patient, but also to reduce

[3] The Association of Anaesthesiologists of Malta (AAM). Information for relatives of patients in Intensive Care Unit [Internet]. Malta: AAM; 2016 [cited 2021 August 15]. Available from URL: http://aam-malta.org/2017/03/06/intensive-care/#ic-sec6

[4] Duke University Medical Centre. What is Evidence-Based Practice (EBP)? [Internet]. USA: 2018 [cited 2021 August 15]. Available from URL: http://guides.mclibrary.duke.edu/c.php?g=158201&p=1036021

the risk of developing severe adverse drug reactions (ADRs) which may prolong recovery (Zhou et al, 2018).

1.2 Drug Therapy in Anaesthesia

Therapy in anaesthesia, including treatment used in the intensive treatment unit should be based on pharmacological properties of the drug and must aim to meet the individual needs and requirements of the patient. The type of drug used, its dose, together with its dosage form and route of administration should be analysed thoroughly. The interplay between altered drug pharmacokinetics and pharmacodynamics must be highly considered in choosing the ideal drug (Narayanan et al, 2016). Care must be taken when adjusting medications and their doses, since a balance between reaching and maintaining effective therapeutic levels of the drug and entering the side effect profile of the drug is difficult, but possible to achieve if rationalised thought and discussions with allied health professionals are carried out. This enables a more holistic course of action. In certain cases, inadequate assessment and treatment of pain may occur as a result of healthcare professionals' overcautiousness in terms of concerns over patient safety, so as to avoid the interactions brought about from the drug's side effect profile together with any drug-drug interactions that may occur (Wheeler, 2005).

Maintaining an optimal level of comfort and safety for patients undergoing surgery is given great importance. Critically ill patients suffer from a variety of organ dysfunctions as a result of their life-threatening condition and thus require treatment with a range of various drugs

such as sedatives, analgesics, neuromuscular blockers and anti-microbials, amongst several other drugs and drug-classes (Power et al, 1998).

An evidence-based approach to clinical practice is adopted in order to provide the most efficient care possible. This mode of practice aims to respect patient values, by making the most of clinical expertise and applying clinically relevant research to current modes of practice (Sacket, 1997). When these three values are integrated, they can be regarded as the three pillars of evidence-based practice, which may be defined as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research" (Sacket, 1997). In this way, an enhanced clinical outcome may result, improving patient quality of life (Black et al, 2001; Murray et al, 2008).

1.2.1 Non-Steroidal Anti-Inflammatory Drugs

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have long-lasting therapeutic effects which make them serve as good analgesic, anti-pyretic, and anti-inflammatory agents. Their pharmacological effects are a result of reduction in prostaglandin production by inhibiting cyclo-oxygenase (COX) enzymes. Different NSAIDs function via different COX pathways and as a result possess different side effect profiles. NSAIDs may block either COX-1, COX-2, or both COX pathways in order to produce their analgesic effect. Non-selective (inhibit both COX-1 and COX-2) NSAIDs however may cause platelet aggregation inhibition resulting in the increased risk of bleeding post-surgery. This side effect is mainly due to

COX-1 inhibition. For this reason, the use of selective COX-2 inhibitors such as celecoxib, is favored due to their reduced side-effect profile. Celecoxib is a drug licensed for pain and inflammation in osteoarthritis. Care must be taken in patients suffering from GI bleeding and ulceration since it may exacerbate their condition. NSAIDs are to be used with caution in ITU due to their antiplatelet activity and likelihood to cause bleeding and renal insufficiency (Wheeler, 2005; Joint Formulary Committee, 2021; Moore et al, 2011).

1.2.2 Perioperative analgesia

The prodrug of valdecoxib, more commonly known as Parecoxib, is a selective inhibitor of cyclo-oxygenase-2 (COX-2) which is generally used in the short-term management of acute post-operative pain. It is given via a deep intramuscular or intravenous injection and is contra-indicated in patients suffering from GI complications, IHD, and inflammatory bowel disease. This potent, multimodal analgesic drug is used in order to reduce the side effects caused by opioid use. Thus, the use of this COX-2 inhibitor is used preferentially to opioids (Joint Formulary Committee, 2021; Liu et al, 2019). However, it is not used locally[5]. Celecoxib, also a COX-2 inhibitor, is marketed as Celebrex® and is found on the local market. It is administered orally as 100mg or 200mg hard capsules.[6]

[5] Malta Medicines Authority (MMA). Parecoxib products P03 Annex [internet]. Malta: MMA;2013 [cited 2021 August 14]. Available from: http://www.medicinesauthority.gov.mt/file.aspx?f=333

[6] Electronic Medicines Compendium (eMC). Celecoxib 100mg hard capsules - Summary of Product Characteristics (SmPC) [Internet]. UK: Datapharm Ltd.; 2019 [cited 2021 August 14]. Available from: https://www.medicines.org.uk/emc/product/3423/smpc#INDICATIONS

1.2.3 Alpha-adrenergic receptor agonists

Dexmedetomidine is a new generation drug belonging to the highly selective alpha-adrenergic receptor (α2-AR) agonist. This drug acts as both a sedative and analgesic agent, allowing for conscious sedation and analgesia. One of its many therapeutic indications is that of reducing delirium and agitation – factors that are highly prevalent within an intensive care setting. This drug is approved for short -term use only since its long- term use may produce bradycardia. A distinguishable advantage for the use of this drug is that it may be used in patients suffering from respiratory depression – a well-known side effect which may be brought about through the use of opioid drugs. Thus, this drug may promote quick recovery and premature weaning in patients on mechanical ventilation since it has shown to improve respiratory function. Besides its use in analgesia and sedation, dexmedetomidine may also be used in perioperative settings. Additional advantages of dexmedetomidine include its anxiolytic and cardiovascular stabilising effects (Kaur and Singh, 2011).

1.2.4 Opiates

Codeine phosphate is a drug belonging to the opiate family, which is used in the treatment of mild-moderate pain. This prodrug is used in a vast majority of patients and is metabolised into its main metabolite morphine, ultimately enabling it to produce its analgesic effect. Recurrent use of opioids tends to result in dependence; both physical and psychological. This is not commonly seen in therapeutic use; however, it is advisable to be cautious when prescribing such drugs to patients having a history of drug dependence (Benini and Barbi,

2014; Joint Formulary Committee, 2021). Opiates such as codeine are commonly combined with non-opioids like paracetamol. This combined therapy (1000mg paracetamol, 60mg codeine) increases post-operative pain relief, but may alter the incidence of adverse events (Toms et al, 2009). Intravenous Paracetamol provides effective pain relief in approximately 36% of patients suffering from post-operative pain (McNicol et al, 2016).

1.3 Anaesthesia

Distress is a prevalent factor experienced by patients in ITU and is mainly attributed to the element of pain caused by myriad factors. Anaesthetic agents thus come into play in order to relieve patients from such pain via sedation (Narayanan et al, 2016). The three aspects of anaesthesia; hypnosis, analgesia, and relaxation are commonly incorporated to ensure a state of balanced anaesthesia. This might not be acquired with the use of a single agent only, so several different types of drugs are given together, some of which are short-acting opioids of the analgesia family (Joint Formulary Committee, 2021).

1.3.1 General Anaesthesia

Propofol is the most widely used intravenous general anaesthetic in adults and children. It merits a rapid recovery and is used for sedation during diagnostic procedures as well as to suit sedative purposes in adults in terms of intensive care. It may be used for sedation of ventilated patients in intensive care via injection, or to maintain a sedative state for surgical

and diagnostic processes. Care must be taken in patients suffering from cardiac complications, respiratory impairment and raised intracranial pressure. Moreover, prolonged infusion of this anaesthetic drug may result in Propofol infusion syndrome which may give rise to potentially fatal effects (Joint Formulary Committee, 2021).

1.3.2 Anaesthesia adjuvants - Sedative Drugs

Drugs belonging to the benzodiazepine family, which may be referred to as sedative-anxiolytics, aid to reduce the fear and anxiety caused prior to surgical interventions, together with providing relief by promoting amnesia. Within ITU, they are used for sedation particularly in patients on assisted ventilation. An example of a drug belonging to this class is diazepam which produces mild effects of sedation and amnesia but is a long-acting drug having active metabolites. Lorazepam and midazolam are also classified under this class with the former being the most potent amnestic agent (Wheeler, 2005; Joint Formulary Committee, 2021). Another drug licensed for sedation in ITU is dexmedetomidine which is an alpha2-adrenergic agonist. This drug is administered intravenously and is generally indicated in patients when a response following a verbal stimulation is required (Joint Formulary Committee, 2021).

1.3.3 Neuromuscular blockade

Neuromuscular blocking drugs used in anaesthesia are sometimes also referred to as muscle relaxants. Anaesthetic properties are exhibited through specific blockade of neuromuscular

junctions giving rise to adequate relaxation of the muscles of the abdomen and diaphragm. Moreover, this causes muscles of the vocal cords to relax enabling the insertion of a tracheal tube. This is a common procedure in ITU and thus the use of these drugs is necessary. Assisted ventilation is an important requirement with the use of neuromuscular blockers until the offending drug is inactivated or antagonized. Without adequate ventilation, respiratory failure would result, leading to patient death (Wheeler, 2005; Joint Formulary Committee, 2021).

Non-depolarising neuromuscular blocking drugs also form part of the neuromuscular blockade family. These are competitive muscle relaxants having a slower onset of action (ranging from 15 minutes to 120 minutes) and have no analgesic or sedative effects, and thus are not considered to trigger malignant hyperthermia. Intubation is facilitated by the use of drugs belonging to this class. The drug type itself is chosen depending on its onset of action, duration and side effect profile, keeping any background conditions the patient suffers from in mind, in order to prevent any negative interactions. A named drug includes pancuronium bromide, which is used in intensive care since it has a long duration of action and therefore suits patients on long-term mechanical ventilation. This amino-steroid neuromuscular blocking drug is not associated with ganglionic blockade or vagolytic activity but histamine release may still occur (Joint Formulary Committee, 2021).

Depolarising neuromuscular blocking drugs such as suxamethonium chloride have the most rapid onset of action in comparison to other neuromuscular blocking drugs. They are thus ideal in situations where a fast onset of action accompanied by a brief duration of action is required. Such a case is during tracheal intubation. Depolarising neuromuscular blocking

drugs differ to their non-depolarising counterparts in-that their actions are irreversible and recoveries spontaneous. suxamethoinum chloride works by mimicking acetylcholine at the neuromuscular junction resulting in neuromuscular blockade as a result of slower hydrolysis and prolonged depolarisation (Joint Formulary Committee, 2021).

1.3.4 Perioperative Sedation

Sedation of patients usually occurs in order to reduce fear and anxiety, minimise the effects of pain as well as to reduce movement. Choice of drugs is highly dependent on the intended procedure since some procedures may tend to be more successful under anaesthesia. The patient must, at all times, be monitored to a great degree of care especially when sedatives are given. Dexmedetomidine is a drug indicated for the maintenance of sedation within ITU. It is given via an IVI and should be administered solely by professional personnel who have adequate training and experience in airway management and anaesthesia (Joint Formulary Committee, 2021).

1.3.5 Malignant hyperthermia

This is a rare complication that arises through the use of anaesthetic agents and is characterised by elevated body temperatures, muscle rigidity together with tachycardia and acidosis. It is mainly attributed with the use of volatile anaesthetic agents and is treated with dantrolene sodium (Joint Formulary Committee, 2021).

1.4 Aims and Objectives

To collate evidence from literature regarding indications and advantages of celecoxib, parecoxib and dexmedetomidine, to obtain local clinicians' perspective via online questionnaire towards the value of implementing selected drugs on the local formulary.

Chapter 2

Methodology

2.1 Overview of Methodology

The methodology was split into sections as summarised in Figure 1.

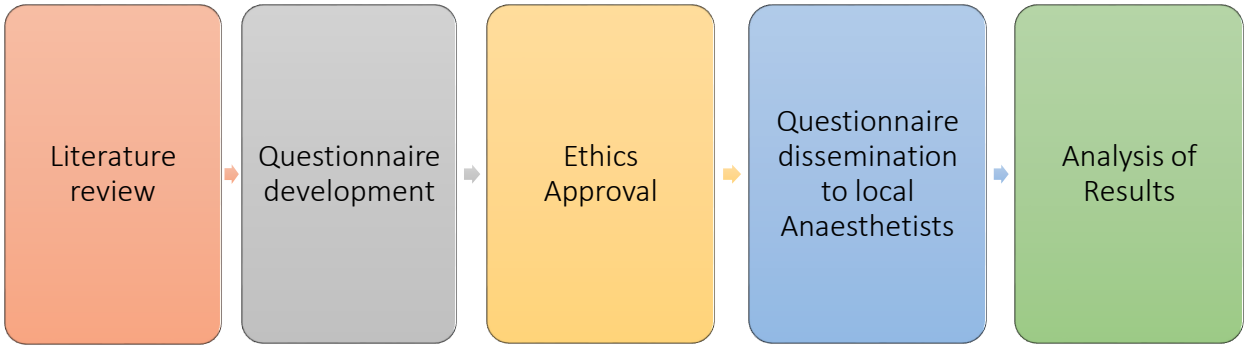

Figure 1: Summary of study-plan

2.1.1 Retrieval of literature

A literature review focusing on celecoxib and parecoxib was carried out in order to identify established guidelines for their use. Several online databases such as HyDi, the National Center for Biotechnology Information (NCBI) and the Cochrane Database of Systematic Reviews (EBSCO) were used to gather relevant material. Information regarding pharmacokinetic profiles were obtained using PubMed and the advantages and disadvantages regarding their use were collated. Local availability in terms of authorisation and licensing for local use within the private and public sector was obtained through the Malta Medicine's Authority (MMA). A literature search regarding use of dexmedetomidine was collected through electronic published database and drug information sources, such as the Electronic Medicines Compendium (EMC) and the British National Formulary (BNF) respectively.

2.1.2 Comparison

Comparison of COX-2 inhibitors celecoxib and parecoxib was carried out using the Summary of Product Characteristics (SPC) for the respective drugs and the data obtained was tabulated to ease the comparison. The features compared were trade name, dosage and dosage form, drug solubility, drug indications and contra-indications.

2.2 Ethics Approval

Prior to disseminating the questionnaire, ethics approval was obtained by the Faculty Research Ethics Committee (FREC), following the study's endorsement by Prof Lilian Azzopardi, Head of Department of Pharmacy at University of Malta and Dr Carmel Abela, Chairperson of Anaesthesia at Mater Dei Hospital. The UREC form as per Appendix 2 guided this study to only require FREC Records as no identifiable patient information nor responder demographics were required for this study.

2.2.1 Participant Information Letter

A participant Information Letter was sent to all applicants along with the questionnaire. The information letter briefed the participants on the contents of the questionnaire and ensured anonymity. The researcher did not contact the participants directly, but was in contact with the secretariat of the Department of Anaesthesia at Mater Dei Hospital, who then distributed the link to the questionnaire to all anaesthetists within the department. Participants were

ensured that their contribution was voluntary and were in a position to withdraw from the study at any point before submission. They were also notified that all results and data will be erased once the study is complete. Contact details of both the researcher and project supervisor were provided in case any of the participants requested further detail.

2.3 Online questionnaire

An online questionnaire was developed on Google Forms. The questionnaire, available in Appendix 1 dealt with gathering attitudes and opinions of anaesthetists practicing at Mater Dei Hospital, focusing on the value that celecoxib, parecoxib, and dexmedetomidine may add to the local formulary. The questionnaire was comprised of both open and close-ended questions. This was done in order to ease the questionnaire flow as well as to receive straightforward answers. The open-ended questions enabled participants to provide reasons for their answers whilst the close-ended questions were set on a five-Likert scale or included tick-boxes.

2.3.1 Data Collection

The self-designed online questionnaire consisted of 18 questions, fifteen of which were obligatory. Data collection took place throughout July-Mid August 2021, three reminders were sent out and a total of 18 out of 105 participants responded.

2.4 Data Analysis

The data was analysed using IBM® SPSS® Version 27. Since the data collected was in the form of text, pre-coding was necessarily carried out in order to convert text into numerical data for analysis by the statistical tools. The numerical data was inputted into Microsoft Excel® for Mac Version 16.47.1. Results from SPSS® were displayed in the form of tables, and bar graphs depending on the data being analysed. The open-ended questions were analysed descriptively according to the themes identified.

Two types of statistical tests were used to analyse the results using IBM® SPSS®. The Chi squared test was used to investigate the association between two categorical variables. One of these variables specified the drug (celecoxib, parecoxib, dexmedetomidine) while the other variable described priority, perceived change and previous experience.

The Friedman test was used to compare mean rating scores assessing perceived value and clinical improvement. These mean rating scores ranged from 1 to 5, where 1 corresponded to ‘not at all’ and 5 corresponded to ‘Extremely’. For this study, the 0.05 level of significance was employed.

Chapter 3

Results

3.1 Evaluation of Celecoxib, Parecoxib and Dexmedetomidine

Both celecoxib and parecoxib are approved for the relief of acute postoperative pain. They have similar pharmacological properties but exhibit lower gastrointestinal side effects relative to Non-Steroidal Anti-Inflammatory Drugs that also target COX-1. Celecoxib is highly COX-2 specific but has reduced aqueous solubility thereby limiting its dosage options[4]. Parecoxib, the water-soluble prodrug of valdecoxib, is the only injectable cyclo-oxygenase-2 inhibitor (Maxwell and Nathanson, 2006). Though no evidence indicates superior degrees of pain relief between the two, parecoxib offers advantages in the immediate post-operative scenario, when oral administration is not possible, such as in patients under anaesthesia, in patients having poor oral absorption following GI surgery and in post-operative nausea and vomiting. Parecoxib has also been proven to be more effective than celecoxib following orthopaedic surgery (Zhuang et al, 2016).

Dexmedetomidine, the new generation drug belonging to the highly selective Alpha-2 Adrenergic Receptor (α2-AR) agonist group, acts as both a sedative and analgesic agent, allowing for conscious sedation and analgesia. One of its many therapeutic indications includes reducing delirium and agitation. It may also be used in perioperative settings and has shown to promote quick recovery and premature weaning in patients on mechanical ventilation since it improves respiratory function (Kaur and Singh, 2011).

[4] National Center for Biotechnology Information. PubChem Database. Celecoxib, CID=2662, https://pubchem.ncbi.nlm.nih.gov/compound/Celecoxib (cited March 202).

A study by Keating, 2015 renders dexmedetomidine more ideal at reducing delirium when compared to patients on propofol, midazolam or remifentanil. Its cardiovascular effects are inversely proportional in that a reduction in heart rate occurs as dexmedetomidine blood concentration rise, until reaching a plateau of 3.2-5.1ng/ml, where it is found to stabilise. Moreover, since no cognitive decline and no rebound tachycardia or hypertension is caused upon dexmedetomidine discontinuation, it is considered beneficial for use in ITU patients, especially since it is considered to have a good tolerability profile.

3.2 Statistical Results from Questionnaire

Different question types, including both open and close-ended answers required different analytical tools which were grouped and sectioned below.

3.2.1 Analysing perceived value for drug introduction

The drug deemed most valuable for inclusion on local formulary was dexmedetomidine, having a mean preference score of 4.6. This was followed by parecoxib, scoring 4.2 and celecoxib scoring 3.9. The Likert scale was set from 1 to 5 with 1 regarded as ‘not valuable at all’ and 5 regarded ‘extremely valuable’. The Friedman test was used to analyse the mean scores obtained for each drug, shown in Table 1. The p value obtained was 0.034 therefore a significant difference in preference was noted between the drugs.

Table 1: Drug preference scores

	Sample size	Mean score	Std. Deviation	Minimum	Maximum
Celecoxib	18	3.944	.802	2	5
Parecoxib	18	4.167	.924	2	5
Dexmedetomidine	18	4.611	.608	3	5

$X^2(2) = 6.745$, $p = 0.034$

Figure 2 displays the disjointed confidence intervals between dexmedetomidine and celecoxib. The confidence intervals between dexmedetomidine and celecoxib are disjointed, thus confirming a statistical difference between the drugs. The largest overlap can be seen between celecoxib and parecoxib, and slightly less with parecoxib and dexmedetomidine. Celecoxib and dexmedetomidine however have an even smaller overlap.

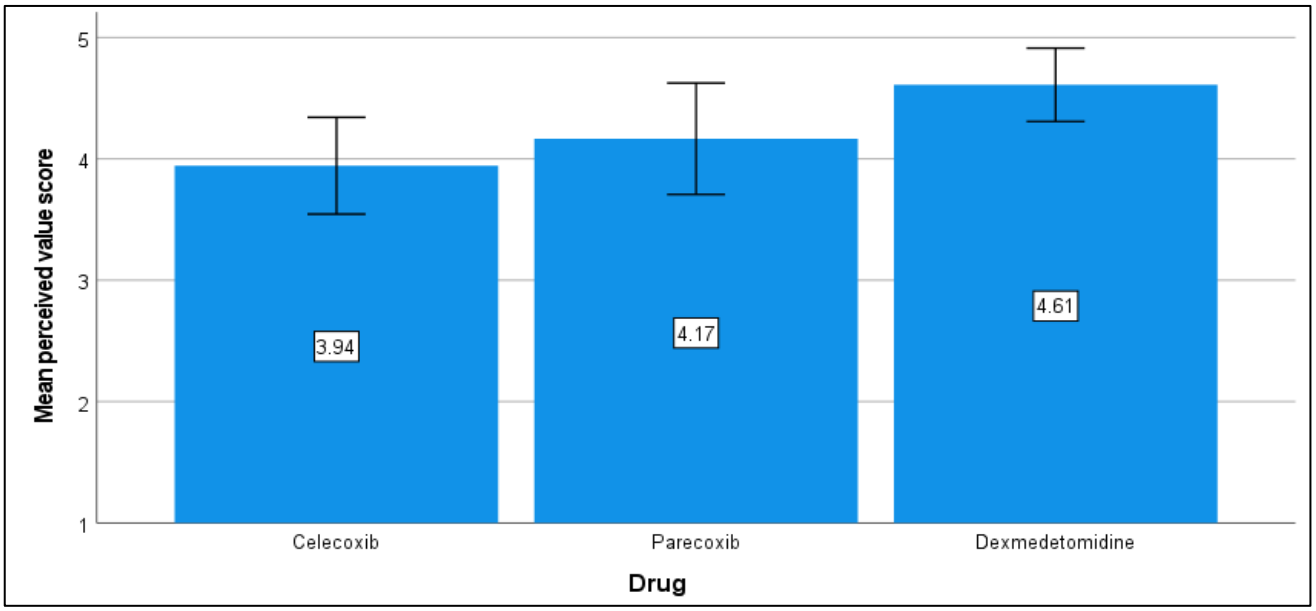

Figure 2: Perceived value scores for celecoxib, parecoxib, dexmedetomidine (n=18)

3.2.2 Analysing drug introduction priority

Celecoxib ranked highest percentages in the second place, preceded by dexmedetomidine and parecoxib which both ranked high percentages in first place, therefore are regarded to be given higher priority for introduction on the local formulary than celecoxib. Having a p-value of 0.008 there was a significant difference between the ranking of parecoxib and dexmedetomidine with respect to celecoxib. All three drugs ranked similarly in the third place, with percentages of approximately 28, 33, and 39 for dexmedetomidine, celecoxib and parecoxib respectively. Parecoxib was ranked highest priority, with 50% of the participants voting 'first', followed by a close-second with dexmedetomidine scoring 44.4%.

Table 2 demonstrates results obtained from the Chi squared test used to determine which drug obtained highest ranking for introduction on local formulary.

Table 2: Drug introduction priority

			Priority			
			First	Second	Third	Total
Prioritise the introduction of the following drugs on the local formulary according to need	Celecoxib	Count	1	11	6	18
		Percentage	5.6%	61.1%	33.3%	100.0%
	Parecoxib	Count	9	2	7	18
		Percentage	50.0%	11.1%	38.9%	100.0%
	Dexmedetomidine	Count	8	5	5	18
		Percentage	44.4%	27.8%	27.8%	100.0%
Total		Count	18	18	18	54
		Percentage	33.3%	33.3%	33.3%	100.0%

$X^2(4) = 13.667$, $p = 0.008$

Clustered Bar Graph shown in Figure 3 identifies drug introduction priority according to local need. This data complements the figures found in Table 2 and exemplifies which drug should be given highest priority for introduction.

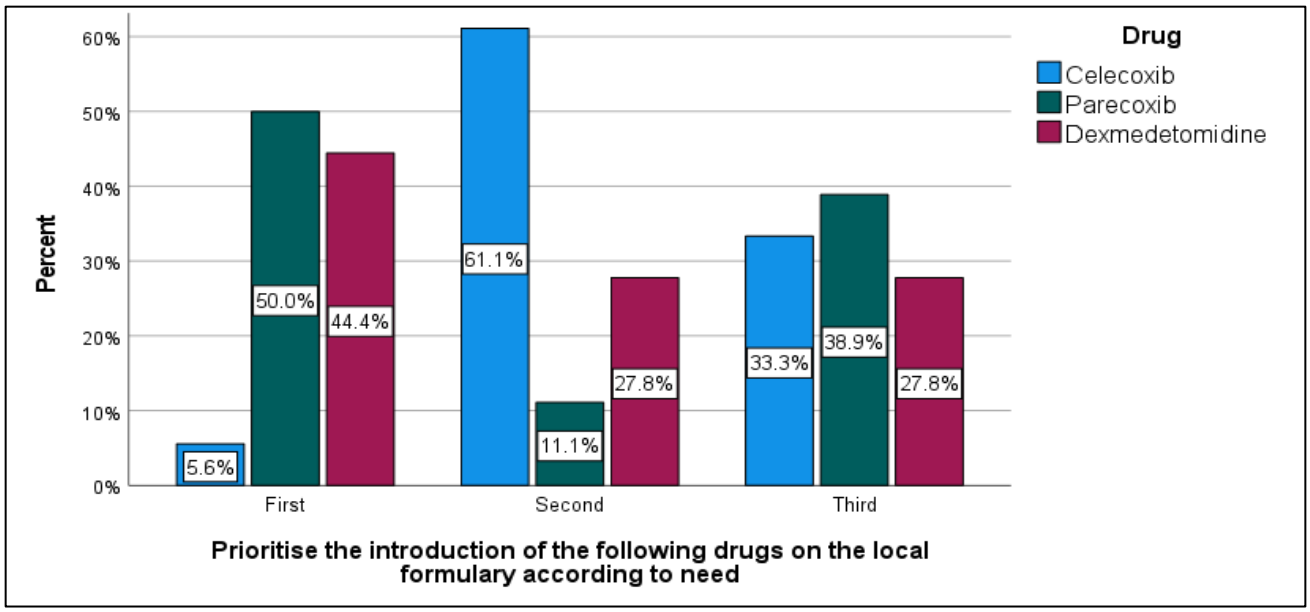

Figure 3: Drug introduction priority (n=18)

3.2.3 Analysing patient populations best suited for use of celecoxib

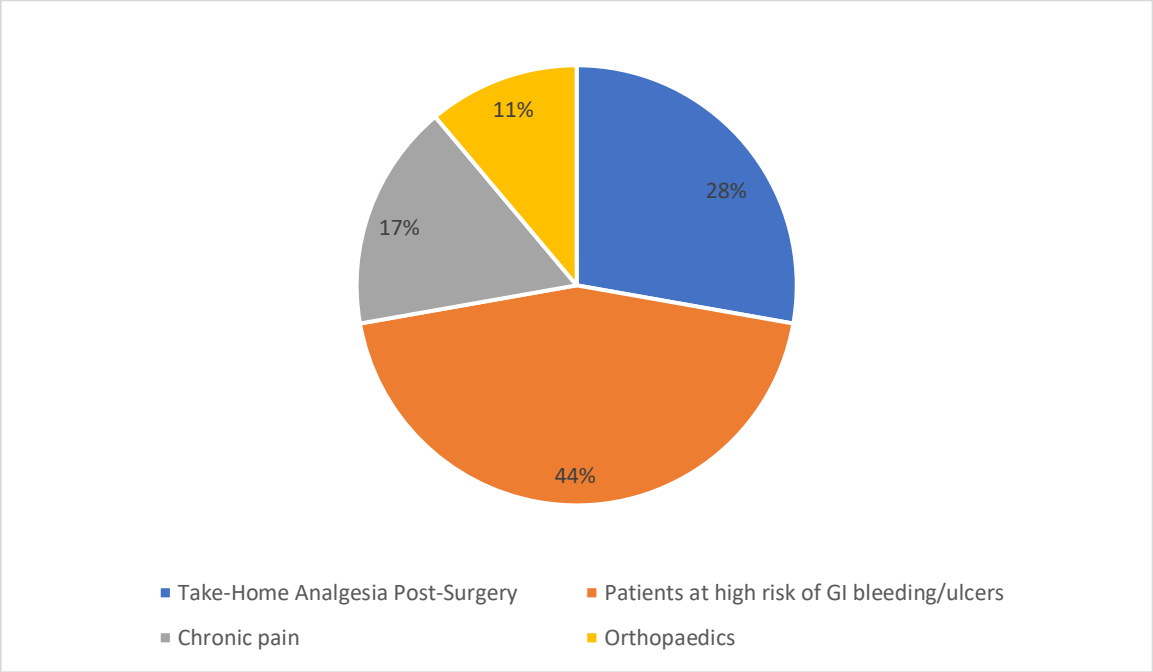

Figure 4: Patient populations best suited for use of celecoxib (n=18)

The patient cohort ranked most suitable for use of celecoxib was in patients at high risk of GI ulcerations, thus requiring a gentler, more selective NSAID on the stomach. This patient cohort received highest number of votes (seven votes in total) which amounted to 44%. Five out of 18 respondents regarded celecoxib most suitable for take-home analgesia post-surgery, whilst 4 out of 18 respondents rendered celecoxib most suitable for use in chronic pain, e.g., pain of inflammatory origin. The remaining 2 out of 18 participants ranked orthopaedics as the most suitable indication for celecoxib.

3.2.4 Analysing patient populations best suited for use of parecoxib

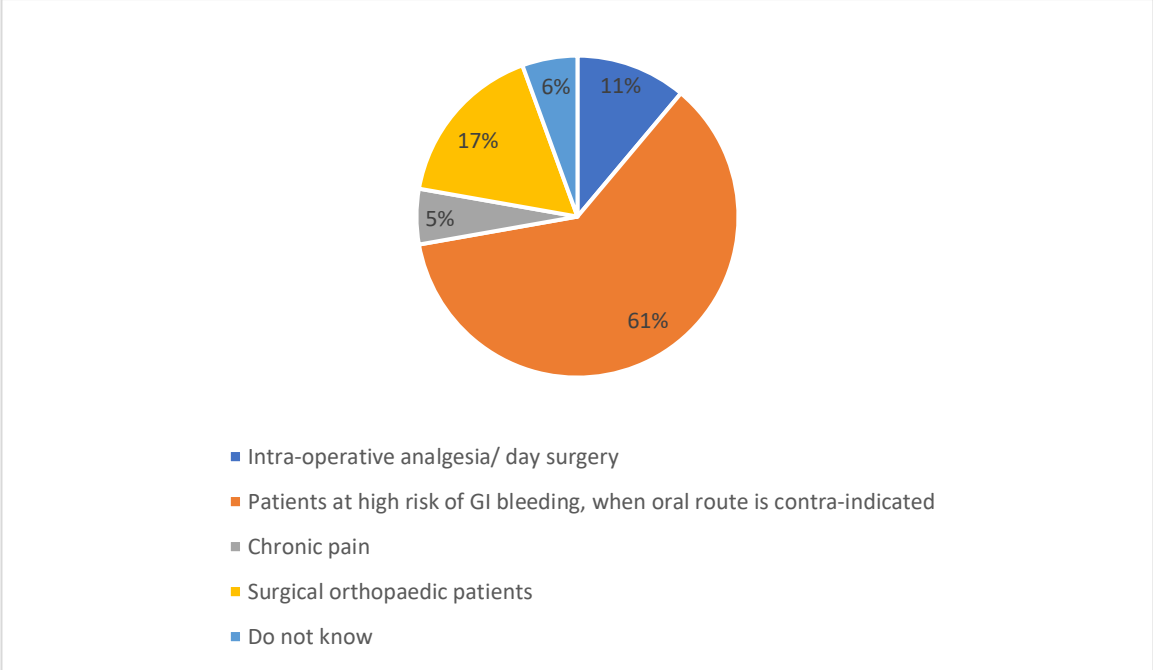

Figure 5: Patient populations best suited for use of parecoxib (n=18)

The patient cohort ranked most suitable for use of parecoxib was in patients at high risk of GI ulcerations, thus requiring a gentler, more selective NSAID on the stomach, particularly in cases when the oral route is contra-indicated. This patient cohort received highest number of votes (11 votes in total) which amounted to 61%. Two out of 18 respondents regarded parecoxib most suitable for intra-operative analgesia for use during day surgery amounting to 11% of the votes. One respondent voted chronic pain as best suited indication for use of parecoxib, and another participant wrote 'do not know'. Seventeen percent of the votes were targeted towards use of parecoxib in orthopaedic patients, with 3 out of 18 votes.

3.2.5 Analysing patient populations best suited for use of dexmedetomidine

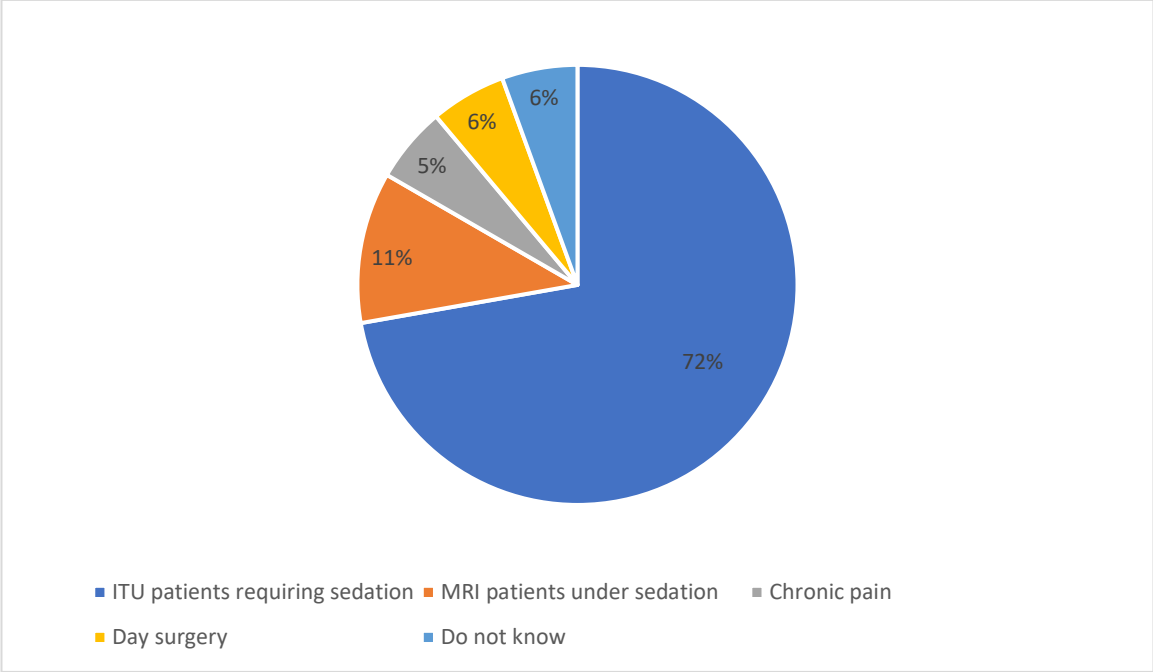

Figure 6: Patient populations best suited for use of dexmedetomidine (n=18)

The patient cohort best suited for use of dexmedetomidine was in ITU patients requiring sedation, in those ITU patients difficult to sedate, and during weaning from ventilation without respiratory depression. This cohort received the highest number of votes, 13 out of 18 in total, amounting to 72%. Two out of 18 participants mentioned MRI patients under sedation, which totals to 11% of the votes. The remaining sectors each gained one vote each and involved patients suffering from chronic pain, patients undergoing day surgery and 'do not know'.

3.2.6 Analysing perceived change in clinical outcomes with the introduction of celecoxib, parecoxib and dexmedetomidine

Dexmedetomidine obtained the highest score (4.4) whilst celecoxib obtained the least score, scoring 3.5, thus a significant difference was noted between the drugs and the p value obtained was less than 0.001 confirming the statistical difference present. The Friedman test was used to analyse perceived improvement in clinical outcome for celecoxib, parecoxib and dexmedetomidine as shown in Table 3.

Table 3: Perceived change in clinical outcome

	Sample size	Mean score	Std. Deviation	Minimum	Maximum
Celecoxib	18	3.50	.985	1	5
Parecoxib	18	3.78	1.114	1	5
Dexmedetomidine	18	4.44	.922	2	5

$X^2(2) = 15.511$, $p < 0.001$

Figure 7 shows the difference in the mean improvement scores of selected drugs. The mean scores ranged from 1-5, the higher the value score given, the higher the expected improvement in clinical outcome. The upper limit of celecoxib and lower limit of dexmedetomidine barely cross, such dis-jointness accounts for the statistical difference between the drugs.

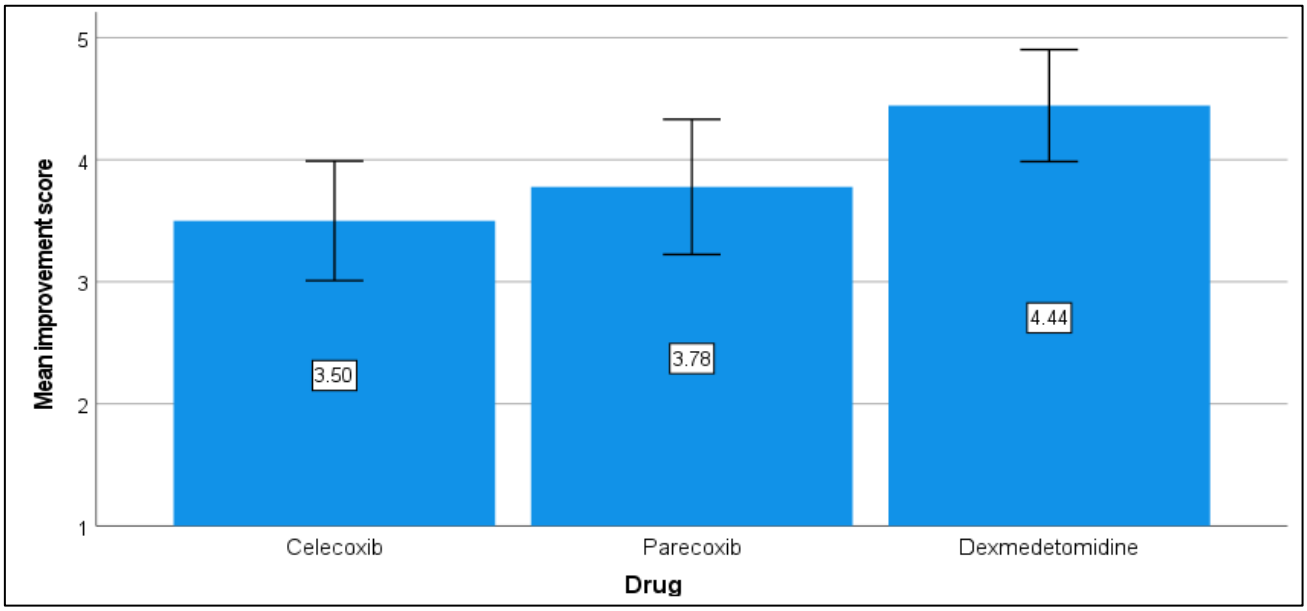

Figure 7: Mean improvement scores in clinical outcome with celecoxib, parecoxib and dexmedetomidine (n=18)

3.2.7 Analysing limitations felt by anaesthetists with the current absence of celecoxib, parecoxib and dexmedetomidine

High percentages were obtained for all three drugs for 'yes, feel limited' whilst lower percentages were obtained for 'no, not limited'. The Chi squared test shown in Table 4, was used to determine anaesthetists' limitations in prescribing in view of the current absence of celecoxib, parecoxib and dexmedetomidine.

Table 4: Prescribing limitations with absence of drugs

			Do you feel limited with what to prescribe with the current absence of drugs		
			Yes	No	Total
Drug	Celecoxib	Count	14	4	18
		Percentage	77.8%	22.2%	100.0%
	Parecoxib	Count	12	6	18
		Percentage	66.7%	33.3%	100.0%
	Dexmedetomidine	Count	15	3	18
		Percentage	83.3%	16.7%	100.0%
Total		Count	41	13	54
		Percentage	75.9%	24.1%	100.0%

$X^2(2) = 1.418$, $p = 0.492$

As shown in Figure 8, the drug found to limit prescribing most was dexmedetomidine, having a percentage of 83.3%, followed by celecoxib which gained 77.8% and parecoxib 66.7%.

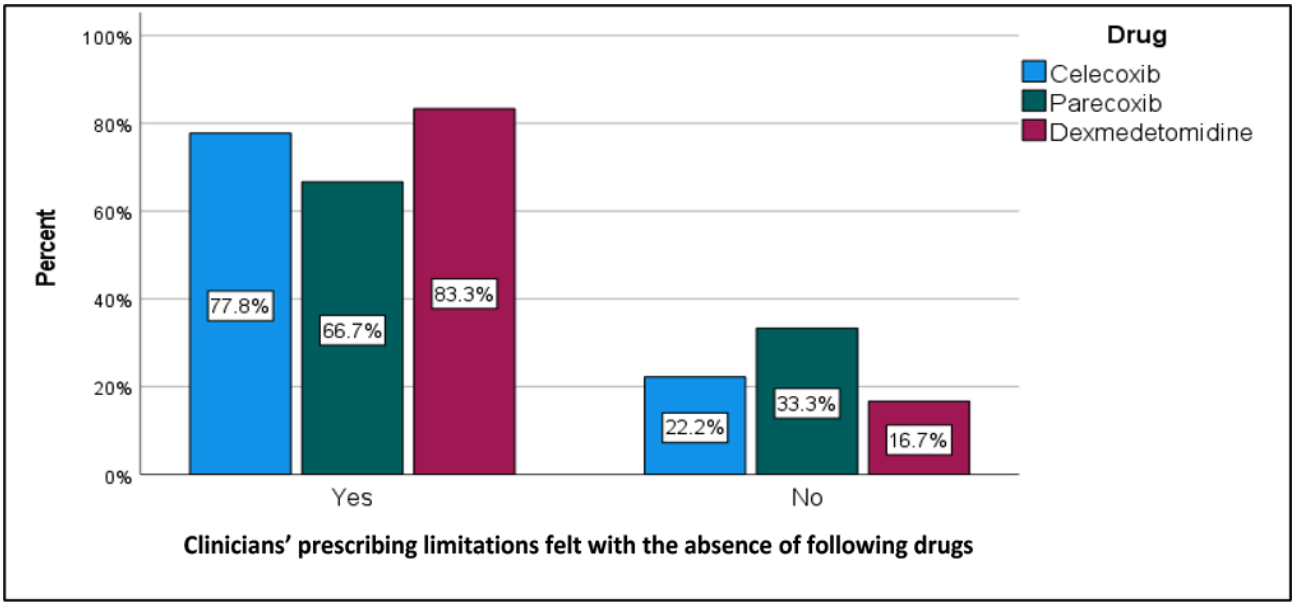

Figure 8: Clinician's prescribing limitations with the absence of drugs (n=18)

3.2.8 Factors influencing drug choice

All 18 participants rendered side effect profile as the main factor influencing drug choice. This was followed by drug familiarity, which gained 12 out of 18 votes (66.7%) and drug cost, amounting to 61.1% of the votes (11 on 18 participants). The remaining two factors owing to influencing drug choice were dosing schedule, and 'other', which gained 33.3% and 5.6% respectively, as shown in Table 5.

Table 5: Factors influencing drug choice (n=18)

		Frequency	Percentage
What factors influence drug choice?	Side effect profile	18	100.0%
	Dosing schedule	6	33.3%
	Cost	11	61.1%
	Drug familiarity	12	66.7%
	Other	1	5.6%

3.2.9 Previous experience with use of celecoxib, parecoxib and dexmedetomidine

Most participants have previous experience with parecoxib, as shown in 12 participants, whilst none of the 18 participants had experience with dexmedetomidine. Experience included work and/or training abroad or use in private practice. A high percentage of the votes were attributed towards celecoxib, with previous experience in 11 out of the 18 respondents. The Chi squared test shown in Table 6 was used to assess whether participants had previous experience with use of celecoxib, parecoxib and dexmedetomidine. A

significant association between previous experience and drug choice was noted since the p value obtained from the Chi squared test was much lower than 0.05 level of significance.

Table 6: Previous drug experience

			Do you have previous experience with use of the following drugs?		
			Yes	No	Total
Drug	Celecoxib	Count	11	7	18
		Percentage	61.1%	38.9%	100.0%
	Parecoxib	Count	12	6	18
		Percentage	66.7%	33.3%	100.0%
	Dexmedetomidine	Count	0	18	18
		Percentage	0.0%	100.0%	100.0%
Total		Count	23	31	54
		Percentage	42.6%	57.4%	100.0%

$X^2(2) = 20.146$, $p < 0.001$

The bar graph in Figure 9 complements the data resulting from the chi squared test, displaying the percentage of the participants' experience in relation to the use of celecoxib, parecoxib and dexmedetomidine.

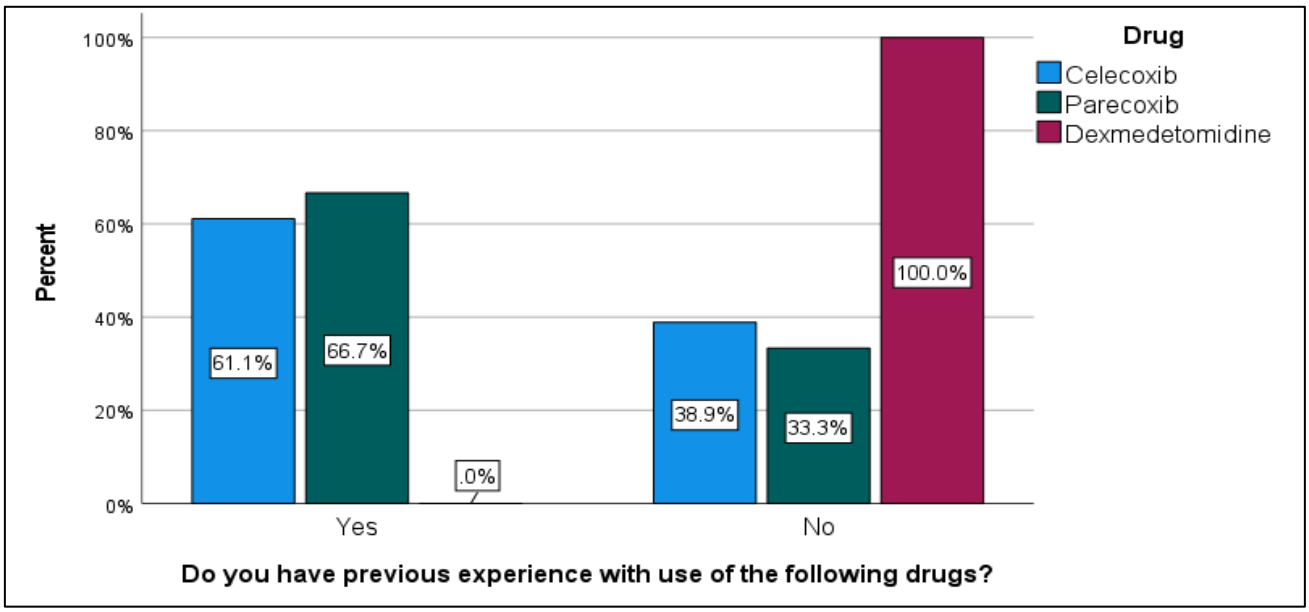

Figure 9: Previous experience with use of celecoxib, parecoxib, dexmedetomidine

3.2.10 Analysing need for adequate training with use of dexmedetomidine

Table 7: Need for training with use of dexmedetomidine

		Frequency	Percentage
Should adequate training be given for dexmedetomidine if it were available for use?	Yes	17	94.4%
	No	1	5.6%

Seventeen out of 18 participants voted for adequate training to be given prior to introduction of dexmedetomidine on local formulary. One respondent (5% of votes) disagreed, claiming that there is no need for training to be given.

Chapter 4

Discussion

4.1 Interpretation of findings

The general consensus amongst local anesthetists practicing within the Department of Anaesthesia at Mater Dei Hospital, indicates that there exists a need for the introduction of celecoxib, parecoxib and dexmedetomidine on the local government formulary to be used for particular indications and patient cohorts. A correlation between information found in literature and results from the online questionnaire distributed, confers that anaesthetists in Malta equally value the drugs in question, and consider their introduction to the formulary valuable to their clinical practice. Celecoxib and parecoxib, being COX-2 specific, prove to be advantageous in patients suffering from gastro-intestinal disorders, particularly ulcers or bleeds (Liu et al, 2019). This owes to the pharmacodynamic properties of these agents in their ability to bypass the negative effects on the stomach, reducing the occurrence of GI ulcerations, as seen more commonly with non-COX selective NSAIDs – of which diclofenac and ibuprofen are amongst those currently available for use in the public health service (Hnepa et al, 2021). In their absence, anaesthetists resort to weak opiates such as codeine when they deem non-COX selective NSAIDs inappropriate, thus exposing patients to other adverse drug effects.

The drug considered most valuable for introduction was dexmedetomidine, followed closely by parecoxib such that it can be said that they are equally desired for first introduction. Besides the sedative and opioid-sparing effects of dexmedetomidine, the latter also holds promise in offering cardio, neuro and renoprotection. It is also beneficial in the reduction of nausea and vomiting in post-operative patients (Afonso and Reis, 2012).

Celecoxib gained the highest percentage of votes in second place. One can infer that such a position resulted due to the fact that celecoxib – being the only formulation available orally (subject to a valid medical prescription) is the only one that benefits out-of-hospital postoperative patients. Furthermore, celecoxib is already available locally within the private market, so its introduction on the local formulary would ease patients' financial burdens whilst improving in-hospital drug availability.

Studies by Jinman et al, 2020, and Zhuang et al, 2016, revealed that parecoxib exhibits an enhanced analgesic effect following orthopaedic surgery when compared to celecoxib. Local anaesthetists were in agreement with this statement and with use of these agents in orthopaedics. The percentage votes obtained by parecoxib was higher than that obtained by celecoxib, with votes of 17% and 11% respectively. The results obtained from questions five and six of the questionnaire correlate with information found in literature.

Local anaesthetists regarded dexmedetomidine best suitable for use in ITU patients requiring sedation, adding that it has great value in patients at risk of respiratory depression and allows sedation during weaning from ventilation. This ties in with Kaur and Singh, 2011 which deemed dexmedetomidine as the alpha-2 agonist which reduces delirium and agitation, without causing respiratory distress. Eleven percent of local anaesthetists also valued use of dexmedetomidine in MRI patients needing sedation. Though a low percentage of local anaesthetists regarded dexmedetomidine beneficial in day surgery and chronic pain, with percentages of 6% and 5% respectively, Tang and Xia, 2017, observed that use of the alpha-2 agonist intra-operatively may reduce incidence and intensity of post-operative pain,

reducing the need for opioid use in managing pain, and ultimately sparing opioid-related adverse effects (Keating, 2015).

Since the aforementioned agents have many advantageous properties to offer, local clinicians feel limited with prescribing in their absence. The drug found to limit clinicians' prescribing most was dexmedetomidine, with 83% of the participants feeling limited without its availability. Following dexmedetomidine was celecoxib, with 78% of participants and lastly parecoxib, which gained 67% of the votes. Parecoxib however was most valuable for nil-by-mouth patients, since being the pro-drug of valdecoxib is more readily soluble and facilitates parenteral administration, thus being most useful when the oral route is contra-indicated (Maxwell and Nathanson, 2006).

Side effect profiles were regarded as the main factor attributing towards choice of drug prescription in this study. Such an importance to these drug properties is further highlighted by clinicians' feeling of being limited in their prescription possibilities in these patient cohorts. This proposes a further incentive for introduction of these agents into the formulary because they have less adverse side effect profiles than their current alternatives, namely diclofenac and codeine. This also goes without saying that having these drugs
also provides additional clinical benefit and would improve patient outcomes, quality of care and possibly reducing hospital costs with respect to needing to care for adverse events incurred by use of standard NSAIDs (such as occurrence of peptic ulceration needing hospital re-admission/lengthened stays following a course of postoperative analgaesia).

Drug familiarity to the prescriber was another factor which come into force when choosing the appropriate drug for patients. This seems to contrast with the overwhelming opinion favouring the introduction of dexmedetomidine given that none of the participants have ever incorporated it in their practice, and that 95% of participants felt that training should be given if this drug is to be introduced. This seemingly contrasting picture contemplates how our local clinicians are very in-tune to dexmedetomidine's intrinsic pharmacological advantages and also their applications to a multitude of potential clinical scenarios. Thus, a period of training would give confidence to our practitioners to for them to apply their theoretical knowledge into fundamental practical experience with dexmedetomidine. The 5% cohort who did not value training to be beneficial represents only one respondent – thus highlighting one of this study's limitations in its small cohort size that influenced final results. Further limitations of this study are described hereunder.

4.2 Limitations

The sample size was the primary limitation considering that 18 out of a total of 105 anaesthetists working in the Public Health Service partook in the study. A larger sample size might have given a more reflective and holistic perspective, increasing the validity of the results as they would be more representative of the entire demographic.

The questionnaire was sent out to all anaesthetists within the Department of Anaesthesia at Mater Dei Hospital, irrespective of their sub-speciality. Bias may be present in answering certain questions based on the background of the participant, in the sense that an intensivist

may be more in favour of introducing dexmedetomidine than a pain specialist, and the latter may prefer the introduction of COX-2 inhibitors rather than dexmedetomidine. This limitation may be overcome by addressing the questionnaire to particular cohorts depending on their speciality within anaesthesia and independently anaylsing the results.

The structure of the questions in the questionnaire, being mainly set on a five-Likert scale, might have also been another limitation to the study given the scale's inherent limitations. Though this scale eases the flow of the questionnaire, it does not indicate whether participants fully understood the meaning behind the questions or gave opportunity for the participant to explain their answers and elaborate on their reasoning. Moreover, participants may be pressed for time and randomly fill in answers without regarding the question and thus influence the results obtained.

The use of an online platform for distributing the questionnaire was another limitation since despite sending out three spaced-out reminders, emails could have been left unread, disregarded or undelivered.

4.3 Recommendations for future research

Questionnaires may be shorter in nature and allow for a better mix of open and close-ended questions possibly followed up by an interview in order to gather further insight and detail. One-to-one correspondence may also pose useful in identifying more lacunae in the lack of

drugs available for use in specific patient populations, and may also give rise to proposing new agents for use locally, beyond those looked into in this study.

This would be even more so enlightening if focus is made to subspecialist anaesthetists individually. A better understanding and need-evaluations for specific drugs and drug classes can be identified in such a segregation. The cohorts may be split up to differentiate intensivists, pain management specialists, and theatre anaesthetists, amongst other possible divisions.

The questionnaire may be addressed to anaesthetists practicing in both private and public sectors as opposed to those working with the NHS locally.

4.4 Conclusion

Results of this dissertation expose the inherent values of celecoxib, parecoxib and dexmedetomidine aspiring towards the introduction of these medications into the local formulary especially in the context of their existing availability and use, both internationally and in the local private sector.

A unanimous agreement to support dexmedetomidine use locally was recognised, followed by much consideration for parecoxib and celecoxib. This owes to Dexmedetomidine's unique sedative and analgesic properties in that it is capable of controlling patient states safely without the risk of respiratory depression. Its widespread use within anaesthesia including

both within the intensive therapy unit and in theatre, makes it no wonder that local anesthetists are attracted towards its introduction and use locally.

Results of this dissertation provide a tangible drive to introduce celecoxib, parecoxib and dexmedetomidine, whilst also correlating with data found in international literature pertaining to these drugs' properties and indications.

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List of Appendices

Appendix 1: Questionnaire distributed to local Anaesthetists

Assessment of Pain Management in Anaesthesia

Gathering attitudes and opinions towards the value of implementing COX-II inhibitors celecoxib and parecoxib, and alpha-2-adrenergic receptor (α2-AR) agonist dexmedetomidine, in the local formulary *Required

1. How valuable is the inclusion of celecoxib to the Government Formulary? *

Mark only one oval.

	1	2	3	4	5	
Not valuable at all	◯	◯	◯	◯	◯	Extremely valuable

2. How valuable is the inclusion of parecoxib to the Government Formulary? *

Mark only one oval.

	1	2	3	4	5	
Not valuable at all	◯	◯	◯	◯	◯	Extremely valuable

3. How valuable is the inclusion of dexmedetomidine to the Government Formulary? *

Mark only one oval.

	1	2	3	4	5	
Not valuable at all	◯	◯	◯	◯	◯	Extremely valuable

4. Prioritise the introduction of the following drugs on the local formulary according to need *

Mark only one oval per row.

	First	Second	Third
Celecoxib	◯	◯	◯
Parecoxib	◯	◯	◯
Dexmedetomidine	◯	◯	◯

5. Which patient population would benefit most from the introduction of celecoxib?

_____

6. Which patient population would benefit most from the introduction of parecoxib?

_____

7. Which patient population would benefit most from the introduction of dexmedetomidine?

_____

8. Do you perceive a change in clinical outcomes locally with the introduction of Celecoxib? *

Mark only one oval.

	1	2	3	4	5	
No improvement	◯	◯	◯	◯	◯	Improved Clinical outcome

9. Do you perceive a change in clinical outcomes locally with the introduction of Parecoxib? *

Mark only one oval.

	1	2	3	4	5	
No improvement	◯	◯	◯	◯	◯	Improved Clinical outcome
No improvement	◯	◯	◯	◯	◯	Improved Clinical outcome

10. Do you perceive a change in clinical outcomes locally with the introduction of Dexmedetomidine? *

Mark only one oval.

	1	2	3	4	5	
No improvement	◯	◯	◯	◯	◯	Improved Clinical outcome

11. With the current absence of celecoxib, do you feel limited with what to prescribe in certain patient cohorts? * *Mark only one oval.*

	1	2	
Yes	◯	◯	No

12. With the current absence of Parecoxib, do you feel limited with what to prescribe in certain patient cohorts? * *Mark only one oval.*

	1	2	
Yes	◯	◯	No

13. With the current absence of Dexmedetomidine, do you feel limited with what to prescribe in certain patient cohorts? * *Mark only one oval.*

	1	2	
Yes	◯	◯	No

14. What factors influence drug choice? *
Tick all that apply.

- [ ] Side Effect profile
- [ ] Dosing Schedule
- [ ] Cost
- [ ] Drug familiarity

Other: ☐ _____

15. Do you have previous experience with use of Celecoxib? (Eg. Work/training abroad, private practice) * *Mark only one oval.*

	1	2	
Yes	◯	◯	No

16. Do you have previous experience with use of Parecoxib? (Eg. Work/training abroad, private practice) * *Mark only one oval.*

	1	2	
Yes	◯	◯	No

17. Do you have previous experience with use of Dexmedetomidine? (Eg. Work/training abroad, private practice) * *Mark only one oval.*

	1	2	
Yes	◯	◯	No

18. Should adequate training be given for dexmedetomidine if it were available for use? *

Mark only one oval.

	1	2	
Yes	◯	◯	No

Appendix 2: Ethical Approvals and Consent Forms

Information Letter

Dear Participant,

My name is Julia Micallef and I am currently reading for a Masters in Pharmacy at the University of Malta. As part of my course requirements I am conducting a research study entitled, Assessment of Pain Management in Anaesthesia. The aim of this study is to collate evidence from literature regarding indications and advantages of celecoxib, parecoxib and dexmedetomidine, to assess value of these drugs for inclusion in the local formulary for use in pain management, and to identify and obtain local clinician's perspective regarding these drugs. Your participation in this study would help gain a better understanding on your perspective on the potential introduction of these drugs. Furthermore, all data collected from this research shall be used solely for the purpose of this study.

Participation in this study is completely voluntary and you are free to accept or refuse to take part without giving a reason. A copy of the information sheet and consent form will be provided for future reference. As a participant, you have the right under the General Data Protection Regulation (GDPR) and national legislation to access, rectify and where applicable ask for the data concerning you to be erased. Once the study is completed and the results are published, all data collected will be erased.

Thank you for your time and consideration. Should you have any questions or concerns do not hesitate to contact me on 99314014 or by e-mail on julia.micallef.16@um.edu.mt or my supervisor Prof Lilian Azzopardi on lilian.m.azzopardi@um.edu.mt.

Yours Sincerely,

Julia Micallef
Researcher

Prof Lilian Azzopardi
Research Supervisor

Request for Approval from Clinical Chairperson

Dear Dr Abela,

You may recall Julia Micallef who is a pharmacy student carrying out a project titled: Assessment of Pain Management in Anaesthesia. As part of her project she would like to disseminate the attached questionnaire to anaesthetists within Mater Dei Hospital.

We would like your permission to disseminate the attached questionnaire. The questionnaire (attached as pdf for your ease of reference) is in google form so a link would ideally be forwarded to avoid having papers lying around. We would appreciate guidance as to whom we can forward the link for eventual dissemination.

For your approval and guidance please,

Thank you for your constant collaboration,

Kind regards

Louise

L-Università ta' Malta

Louise Grech | Senior Lecturer

B.Pharm(Hons)(Melit), M.Phil(Glas), Ph.D(Melit), MRPharmS

Department of Pharmacy

Faculty of Medicine & Surgery
Room 139, Biomedical Building

Approval from Clinical Chairperson

Dear Louise and Julia,

You have my approval.

Thank you,

Dr Abela

Ethics UREC Form

UNIQUE FORM ID: 9220_29062021_Julia Micallef

No self-assessment issues ticked. Submitting to FREC for records.

ETHICS & DATA PROTECTION

PART 1: APPLICANT AND PROJECT DETAILS

1. Name and surname: Julia Micallef

Email Address: julia.micallef.16@um.edu.mt 2. Applicant status: UM student

3. Faculty: Medicine and Surgery

4. Department: Department of Pharmacy

If applicable

5. Principal supervisor's name: Prof Lilian Azzopardi

6. Co-supervisor's name: Dr Louise Grech

7. Name of Degree and Study-unit code: MPharm PHR5123 8. Student number: 272898M

9. Title of research project: Assessment of Pain Management in Anaesthesia

10. Research question/statement & method: The study aims are to collate evidence from literature regarding indications and advantages of celecoxib, parecoxib and dexmedetomidine, to assess value of these drugs for inclusion in the local formulary for use in pain management, and to identify and obtain local clinician's perspective regarding these drugs.

11. Collection of primary data from human participants?

No (PROCEED TO PART 2. SELF-ASSESSMENT)

12. If applicable, explain:

PART 2: SELF-ASSESSMENT Human Participants

1. Risk of harm to participants: 2. Physical intervention:

3. Vulnerable participants:

4. Identifiable participants:

5. Special Categories of Personal Data (SCPD): 6. Human tissue/samples:

7. Withheld info assent/consent:

8. Opt-out consent/assent:

9. Deception in data generation: 10. Incidental findings:

UNIQUE FORM ID: 9220_29062021_Julia Micallef

No self-assessment issues ticked. Submitting to FREC for records.

Unpublished secondary data

11. Was the data collected from human participants?

12. Was the data collected from animals?

13. Is written permission from the data controller still to be obtained?

Animals

14. Live animals out of habitat: 15. Live animals, risk of harm: 16. Dead animals, illegal:

General considerations

17. Cooperating institution: 18. Risk to researcher/s: 19. Risk to environment: 20. Commercial sensitivity 21. Other potential risks:

Self-assessment outcome: No self-assessment issues ticked. Submitting to FREC for records. PART 3: DETAILED ASSESSMENT

1. Risk of harm to participants:

2. Physical intervention on participants:

3. Vulnerable participants:

4. Identifiable participants:

5. Special Categories of Personal Data (sensitive personal data):

6. Collection of human tissue/samples:

7. Withholding information at consent/assent:

8. Opt-out consent/assent:

9. Deception in data generation:

10. Incidental findings:

11. Unpublished secondary data - human participants :

12. Unpublished secondary data - animals:

13. Unpublished secondary data - no written permission from data controller: 14. Lasting harm to animals out of natural habitat:

15. Risk of harm to live animals :

16. Use of non legal animals/tissue:

17. Permission from cooperating institution:

18. Risk to researcher/team:

19. Risk of harm to environment:

20. Commercial sensitivity:

UNIQUE FORM ID: 9220_29062021_Julia Micallef

No self-assessment issues ticked. Submitting to FREC for records.

21. Other issues

21a. Dual use and/or misuse:

21b. Conflict of Interest:

21c. Dual role:

21d. Use research tools:

21e. Collaboration/data/material collection in low/lower-middle income country: 21f. Import/export of records/data/materials/specimens:

21g. Harvest of data from social media: 21h. Other considerations:

PART 4: SUBMISSION

1. Which FREC are you submitting to? : Medicine and Surgery

2. Attachments: Information and recruitment letter*, Data collection tools (interview questions, questionnaire etc.), Letter granting institutional approval from person directly responsible for participants 3. Cover note for FREC :

4. Declarations: I hereby confirm having read the University of Malta Research Code of Practice and the University of Malta Research Ethics Review Procedures., I hereby confirm that the answers to the questions above reflect the contents of the research proposal and that the information provided above is truthful., I hereby give consent to the University Research Ethics Committee to process my personal data for the purpose of evaluating my request, audit and other matters related to this application. I understand that

I have a right of access to my personal data and to obtain the rectification, erasure or restriction of processing in accordance with data protection law and in particular the General Data Protection Regulation (EU 2016/679, repealing Directive 95/46/EC) and national legislation that implements and further specifies the relevant provisions of said Regulation.

5. Applicant Signature: Julia Micallef

6. Date of submission: 29062021

7. If applicable data collection start date: 01072021

8. E-mail address (Applicant): julia.micallef.16@um.edu.mt

9. E-mail address (Principal supervisor): lilian.m.azzopardi@um.edu.mt

10. Conclude: Proceed to Submission

Approval from FREC

Dear Ms Micallef,

Good afternoon and thank you for the UREC Form.

Since your self-assessment resulted in no issues being identified, FREC will file your application for record and audit purposes but will not review it.
Any ethical and legal issues including data protection issues are your responsibility.

Kindly **confirm** that you sent all the documents which you attached to the UREC form together with other documents related to your study.

Kindly note that these documents are also requested for audit purposes.

Regards,

Annalise

L-Università ta' Malta

Annalise Mallia Duca | Secretary

Faculty Research Ethics Committee

Faculty of Medicine and Surgery

Medical School, Mater Dei Hospital

+356 2340 1803

Dear Ms. Mallia Duca,

Thank you for your reply.

I confirm that all relevant documents were attached.

Many thanks,

Julia Micallef

Dear Ms Micallef,

Thank you for your email and good luck with your research!

Regards,

Annalise

L-Università ta' Malta

Annalise Mallia Duca | Secretary

Faculty Research Ethics Committee

Faculty of Medicine and Surgery

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