Final Study Report

Study Title: Comparison of pain and comfort in patients following cardiac surgery: Opioid- morphine managed versus multimodal pain-management (MONDAY)

EU reference number: 2019-000515-84

Clinical Investigation identification number (CIV ID): NA

Study protocol/CIP code: AGO/2019/001

Investigational device / medicinal product: Dexdor 100 microgram/ml (EU/1/11/718/001-002), Fentanyl-Janssen 0,05 mg/ml (BE 091996), Ketalar 50 mg/ml (BE005293), Linisol 1 % (BE166695), Lyrica 75 mg (EU/1/04/279/044), MAGNESIUM SULFATE STEROP 1g / 10ml (BE259271), OxyNorm Instant 10 mg (BE319076), Paracetamol Fresenius Kabi 10 mg/ml (BE537875), TRADONAL 100 mg (BE177615), Ultiva 2 mg (BE181912)

ClinicalTrials.gov identifier: NCT04987372

Sponsor: Ghent University Hospital

Contact details sponsor: C. Heymanslaan 10, 9000 Gent

Coordinating Investigator: dr. Harlinde Peperstraete

Funder: NA

Author: dr. Harlinde Peperstraete

Date of report: 09DEC2022

By signing this final study report, I acknowledge that the information is accurate and complete.

Name and signature Coordinating Investigator: dr. Harlinde Peperstraete .....

Date signature Coordinating Investigator: 9/12/2022

Harlinde Peperstraete

Table of content

1. Introduction

Cardiac surgery performed by sternotomy is associated with moderate to severe acute postoperative pain. Most common analgesic schemes for per- and postoperative pain in cardiac surgery are based on intravenous opioids. However, opioids have several dose-related side effects. In the last decade, much has been written about multimodal pain protocols to treat acute postoperative pain and to prevent postoperative delirium in cardiac surgery. Our goal is to compare standard opioid based regimen to a multimodal pain management to determine which therapy provides the most comfort, the fastest extubation time, the least pain and the least delirium.

2. Objectives of the study

To compare standard "Fentanyl – Tramadol – Paracetamol – Oxycodon" regimen to a multimodal painmanagement "pregabalin- minimal fentanyl-ketamine-lidocain-dexmedetomedine- paracetamol" to determine which therapy provides the most comfort, the fastest extubation time, the least pain and the least delirium.

3. Investigational Medicinal Product

3.1 Medication, producer administration route and dosing

Classic protocol

Medication	Dose	Route	Time of administration
Fentanyl	Max. 15µg/kg	IV	Per-op
Ultiva (Remifentanyl)	0.02-0.1µg/kg/h	IV	Post-op
Paracetamol	4x1g /24h	IV	Post-op
Tradonal (Tramadol)	100mg IV 4/d	IV	Post-op
Oxynorm (Oxycodon)	5-10mg 4-6/d	PO	Post-op (Break through pain)

Multimodal protocol

Medication	Dose	Route	Time of administration
Lyrica (Pregabalin)	75mg	PO	Pré-op
Dexdor (Dexmedetomidine)	0.8µg/kg/h	IV	Per-op / Post-op
Ketalar (Ketamine)	Bolus (0.5mg/kg) + 0.3mg/kg/h	IV	Per-op until stop propofol
Linisol (Lidocaïne)	Bolus (1.5mg/kg) + 1.3mg/kg/h	IV	Per-op until 12h post-op
Magnesium Sulfate	Induction (25mg/kg) + 25mg/kg weaning ECC	IV	Per-op
Fentanyl	2.5µg/kg	IV	Per-op
Paracetamol	4x1g /24u	IV	Post-op
Tradonal (Tramadol)	100mg IV 4/d	IV	Post-op (Break through pain)
Oxynorm (Oxycodon)	5-10mg 4-6/d	PO	Post-op (Break through pain)

3.2 Distributor

Pharmacy department, Ghent University Hospital

3.3 Packaging

Commercially available packaging

3.4 Labelling

Following the rules of both the department of Anesthesia and Intensive Care Unit. In case of tablets packaging is double: the commercially available monopackage is found in little tear-off plastic bags, produced by the pharmacy department of Ghent University Hospital.

3.5 Storage conditions

All medication will be stored by the general recommendations of the pharmacy department of our hospital.

4. Study Protocol Summary

4.1 Study design

Prospective randomised double-blinded (for participant and study staff) study. Each study subject will be observed until 48h after arrival at ICU.

4.2 Inclusion criteria

- Patients undergoing first time cardiac surgery by median sternotomy
- Elective surgery or semi-urgent: there needs to be time to provide 1 hour before surgery the intake of pregabalin
- ≥ 18 years for men
- Women who are in menopause
- Possibility to communicate with the patient to score pain and comfort
- Signed Informed Consent, signed by subject able and willing to provide written informed consent for study participation

4.3 Exclusion criteria

- Urgent surgery
- Women who are in premenopause
- Hypersensitivity to any of the study medication
- In case of direct postoperative revision the patient is NOT excluded.

4.4 Primary endpoint

The primary endpoint of this study is postoperative pain (at rest, when coughing and at movement) at 8-h, 16-h, 24-h, 32-h, 40-h and 48-h after cardiac surgery. Pain is measured by a NRS-scale if the patient is awake, and by the Critical-Care Pain Observation Tool(CPOT) in the sedated patient.

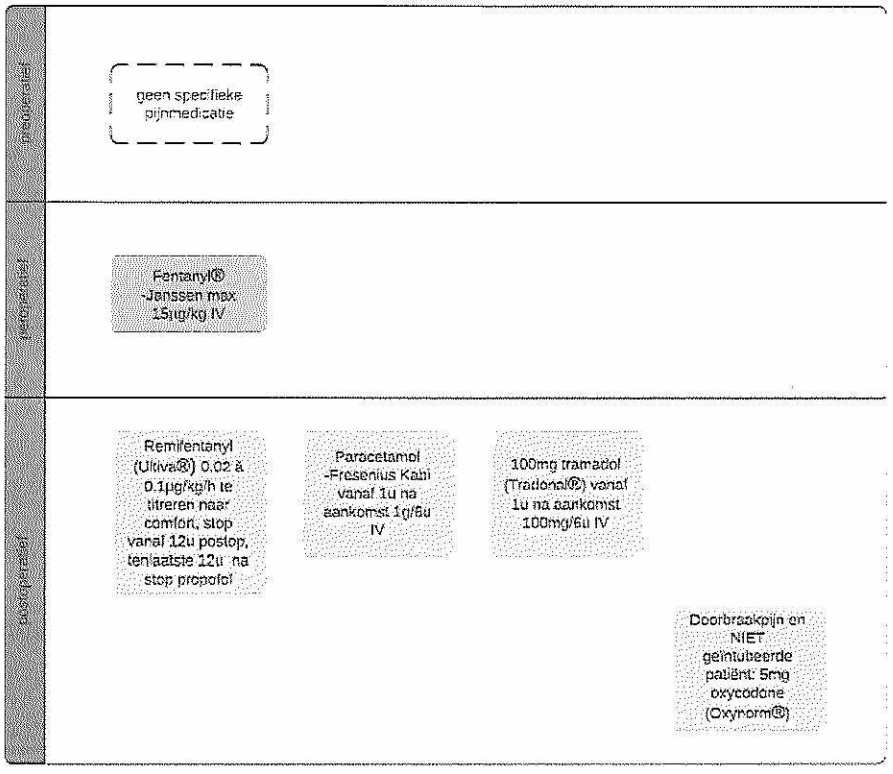
4.5 Secondary endpoints

Secondary endpoints include delirium in the direct postoperative phase measured by the ICDSC-score. Also included in the secondary endpoints are: time till extubation, length of hospital stay, length of stay at the ICU department and total consumption of pain medication registered in mg/kg.

4.6 Procedures

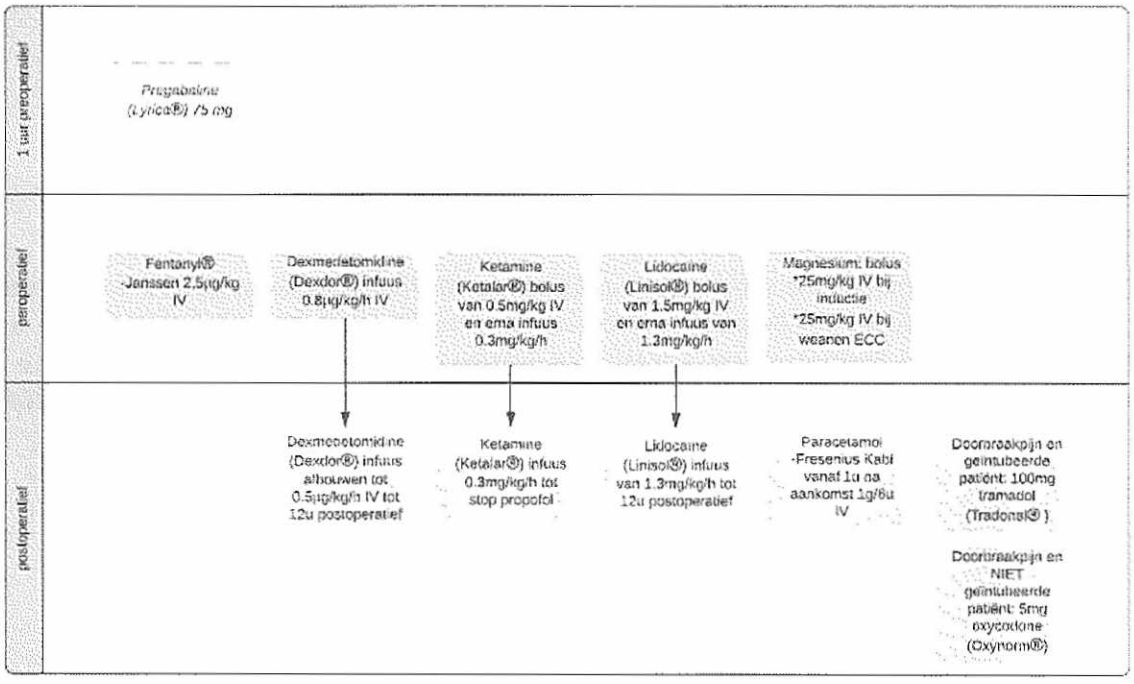
Patients will be randomized in the Classic Protocol or in the Multimodal protocol. A pregnancy test is not standard in women, as we only include women in menopause.

If a patient was assigned to the standard pain protocol, no pain medication was given preoperatively. Induction was also done with Propofol until loss of consciousness and Fentanyl. Fentanyl dose was limited to 15µg/kg IV. Postoperatively, a continuous infusion of Remifentanil was started at a dose of 0.05-0.1 µg/kg/h and stopped 12 h postoperatively. Magnesium 2.5 mg/kg was given once at induction.



In the multimodal pain protocol, patients received Pregabaline 75mg one hour preoperatively. Once in the operating room, a dexmedetomidine infusion was started at 0.8µg/kg/h.

Postoperatively at ICU, the continuous infusion was lowered to 0.5 µg/kg/h and stopped 12 hours postoperatively. Induction of anesthesia was performed with Propofol until loss of consciousness and Fentanyl 1-2 µg/kg. Fentanyl dose was limited to 2.5µg/kg during the peroperative period. If needed, the anesthesiologist was allowed to exceed this dose, as long as it was documented. After induction of anesthesia, a bolus of ketamine 0.5 mg/kg IV was given followed by a continuous infusion of 0.3 mg/kg/h. This continuous infusion was stopped postoperatively at ICU together with the continuous infusion of propofol. Also a bolus of Lidocaine 1.5 mg/kg IV was given at induction followed by a continuous infusion of 1.3 mg/kg/h. This Lidocaine infusion was stopped 12 hours postoperatively. Magnesium was given 25 mg/kg IV at induction and was repeated after weaning of the extracorporeal circulation.



For both groups, postoperative pain management consisted of Paracetamol 1g/6h IV and Tramadol 100mg/6h IV if needed and as long as the patient was ventilated. Once a patient was extubated rescue pain medication was Oxycodone 5mg. No others analgesics were allowed.

4.7 Study participants

All Patients, aged 45 or older, undergoing a first sternotomy for coronary artery bypass graft (CABG) surgery with or without valve replacement requiring cardiopulmonary bypass were candidates for trial inclusion. In women we actively checked for being in menopause to rule out a systematical pregnancy test in women.

Patients with a preoperative left ventricular ejection fraction less than 30%, preexisting cognitive impairment measured by a preoperative MMSE less than 21, Alzheimer disease, Parkinson disease, history of recent seizures, or hypersensitivity to any of the study medications, and patients taking medications for cognitive decline or under chronic pain medication therapy were excluded. Participants who did not speak Dutch were excluded because of their inability to complete the cognitive assessments, which have been extensively validated in Dutch.

4.8 Randomisation and blinding

After informed consent, patients were assigned randomly (1:1) by computer randomization to either a 'standard' pain protocol or a multimodal pain protocol. The attending anesthesiologist was aware of the randomization. Patients and study nurses were blinded to the pain management.

4.9 Monitoring and quality measures

Quality control of data of the CRFs will be done by comparing the data of the original documents with those of the eCRFs by a person who was not associated with filling in the CRFs. All data will be reported in the eCRF files following GCP rules and HIRUZ CTU (Ghent University Hospital) will monitor closely the study. eCRF's will be created by Redcap.

5. Study analysis

5.1 Sample size calculation

Following data were used for sample size calculation: Two independent study groups, continuous endpoints, an anticipated incidence of NRS-score in the standard protocol of 4 vs 3 in the multimodal group, with a standard deviation of 1.5, based on a previous study by Rafiq S. et al [3], a probability of type 1 error of 5% and power of 80%. Two groups of 35 patients were calculated.

5.2 Statistical analysis

Research Electronic Data Capture (REDCap) was used for data collection and included demographic data, information on analgesics and sedatives during the first 48 hours postoperatively, pain scores, patient delirium and cognition assessment data, and adverse events. Data were abstracted from the medical record to assess secondary endpoints.
Statistical analysis was done with IBM SPSS® software, version 26. We used descriptive statistics and used for parametric data: unpaired t-test, or student t-test, for non-parametric data: Wilcoxon's test. For repeated measures of non-independent data, to test for fixed effects, we used linear mixed models type III tests. Level of significance was set at $(p) < 0.05$.

6. Independent Ethics Committee and Competent Authority

Full approval of the protocol and addenda has been obtained from the Central Ethics Committee of the University Hospital Ghent and the FAMHP. For the prolongation of the study, two additional amendments approved by the Central Ethics Committee of the University Hospital Ghent. (schematic overview in the table below)

OVERVIEW APPROVED DOCUMENTS		
Initial submission:	**Approval EC:**	**Approval FAMHP:**
- Protocol v4 dd. 10JUL2019 - ICF dd. 10JUL2019	16JUL2019	15JUL2019

- SmPCs (Dexdor, Fentanyl, Ketalar, Linisol, Lyrica, Magnesiumsulfaat, Oxynorm, Paracetamol, Tradonal, Ultiva) - Labels IMP		
Amendment 1: - Prolongation of the study until 01JUN2021	**Approval EC:** 01JUN2020	**Approval FAMHP:** NA
Amendment 2: - Prolongation of the study until 01DEC2021	**Approval EC:** 13JUL2021	**Approval FAMHP:** NA

7. Results

7.1 Subject enrollment and demographics

Ninety-six patients were successfully enrolled. Baseline characteristics were similar between the two groups. Gender in both groups was 80 vs 82 % males in the multimodal vs opioid group. Mean age was 71.2 vs 70.2 years in the multimodal vs opioid group. Mean BMI was 27.2 vs 27.1 in the multimodal vs opioid group. Baseline Mini Mental State Examination (MMSE) was 27.4/30 vs 27.5/30 in the multimodal vs opioid group.

7.2 Study specific results

The multimodal pain scheme was administered in 46 patients, while 50 patients received the opioid based scheme. After linear mixed model analysis no significant differences were seen in CPOT-score (p=0,305), NRS-score (p=0,182) or consumption in rescue pain medication. Also, for the ICDSC-score no significant difference was found (p=0,267). A significant difference in LOS at ICU was seen (p=0.032) in the opioid group. Time to extubation or LOS at the hospital showed no significant difference between both groups.

8. Safety

No SAEs occurred during the course of this study.

9. Protocol deviations

Subject nr	Date of protocol deviation	Classification *Minor /Major	Description of deviation	Action taken
1	09SEP2019	Major	Fentanyl dose per op was too high for multimodal approach (was 8µg/kg instead of max. 2,5µg/kg) and patient didn't receive magnesium sulphate per-op	Retraining medication scheme multimodal approach
2	09SEP2019	Minor	Patient was randomised to opioid arm, but received magnesium per-op (which isn't prescribed for the opioid approach) patient received a slightly higher dose of fentanyl per-op (16µg/kg instead of 15 µg/kg)	Retraining medication scheme opioid approach
3	10SEP2019	Minor	Patient, randomised to the opioid arm, received per-op 2g magnesium which is not included in the opioid protocol.	Retraining medication scheme opioid approach
4	11SEP2019	Minor	Patient received lidocaine bolus of 50mg (BW is 80kg, so patient received 0,625mg/kg). However in the multimodal protocol, patient should receive a lidocaine bolus of 1,5mg/kg	Retraining medication scheme multimodal approach
5	12SEP2019	Minor	Patient received 2g of magnesium, which is not included in the opioid protocol.	Retraining medication scheme opioid approach
6	12SEP2019	Minor	Patient 6 received 450µg of fentanyl in the multimodal approach (80kg, 5,625µg/kg) which is higher than the prescribed 2,5µg/kg	Retraining medication scheme multimodal approach
Sponsor Deviation	03DEC2021	Minor	Study-specific procedures were performed after 01DEC2022 (approved duration of the trial)	Monitor discussed this with the study team
57, 58, 59, 60, 61, 65 to 68, 74 to 91, 93 to 98, 101	02JUN2022	Critical	ICF procedure: Non-approved version dd. 01APR2019 was used to obtain informed consent	Monitor discussed this with study team + notification to ethics committee. Ethics committee decided that no further action was required.
37	02JUN2022	Critical	ICF: 1st page from non-approved version dd. 23APR2019 (but identical); 2nd page is missing	Monitor discussed this with study team + clarification was added by the PI

Subject nr	Date of protocol deviation	Classification *Minor /Major	Description of deviation	Action taken
Sponsor Deviation	03DEC2022	Minor	Final Study Report not submitted before the legal deadline	Monitor reminded the sponsor team
2,9,12,16,18,22,26,28,29,31,34,36,38,41,44,75,90	/	Minor	Magnesium 2,5 G was administered by the anaesthesiologist in the opioid arm.	None
40,48,66,72,85,90,96	/	Minor	Magnesium 2 G was administered by the anaesthesiologist in the opioid arm. Only Magnesium 2 G is available due to stock break.	None

Medication schemes were not strictly followed by the anaesthesiologist since administration of Magnesium is routinely standard of care.

10. Discussion and overall conclusions

10.1 Results

Ninety-six patients were successfully enrolled after randomization. Baseline characteristics were similar between the two groups.

Gender in both groups was 80 vs 82 % males in the multimodal vs opioid group. Mean age was 71.2 vs 70.2 years in the multimodal vs opioid group. Mean BMI was 27.2 vs 27.1 in the multimodal vs opioid group. Baseline Mini Mental State Examination (MMSE) was 27.4/30 vs 27.5/30 in the multimodal vs opioid group.

The multimodal pain scheme was administered in 46 patients, while 50 patients received the opioid-based scheme. After linear mixed model analysis no significant differences were seen in CPOT-score (p=0,305), NRS-score (p=0,182) or consumption in rescue pain medication. Also, for the ICDSC-score no significant difference was found (p=0,267). A significant difference in LOS at ICU was seen (p=0.032) in the opioid group. Time to extubation or LOS at the hospital showed no significant difference between both groups.

10.2 Discussion

This trial shows a significant difference in LOS in ICU in favor of the opioid group. No significant differences could be found in pain, delirium, intubation time or LOS in hospital between a multimodal analgesic protocol versus an opioid-based analgetic protocol in cardiac surgery by sternotomy. This is not in line with previous studies but is probably because this trial was underpowered. This study shows

that there is a place for multimodal analgesia in cardiac surgery which can serve as a good alternative for opioid-based protocols.

11. References

1. Mueller, X.M., et al., *Pain location, distribution, and intensity after cardiac surgery.* Chest, 2000. **118**(2): p. 391-6.
2. Bigeleisen, P.E. and N. Goehner, *Novel approaches in pain management in cardiac surgery.* Current opinion in anaesthesiology, 2015. **28**(1): p. 89-94.
3. Rafiq, S., et al., *Multimodal analgesia versus traditional opiate based analgesia after cardiac surgery, a randomized controlled trial.* Journal of cardiothoracic surgery, 2014. **9**: p. 52.
4. White, P.F., et al., *Use of a continuous local anesthetic infusion for pain management after median sternotomy.* Anesthesiology, 2003. **99**(4): p. 918-23.
5. Noss, C., et al., *Enhanced Recovery for Cardiac Surgery.* J Cardiothorac Vasc Anesth, 2018. **32**(6): p. 2760-2770.
6. Weinbroum, A.A., *Non-opioid IV adjuvants in the perioperative period: pharmacological and clinical aspects of ketamine and gabapentinoids.* Pharmacol Res, 2012. **65**(4): p. 411-29.
7. Gjeilo, K.H., et al., *Chronic postsurgical pain in patients 5 years after cardiac surgery: A prospective cohort study.* European journal of pain (London, England), 2017. **21**(3): p. 425-433.
8. Pieri, M., et al., *Trials Focusing on Prevention and Treatment of Delirium After Cardiac Surgery: A systematic Review of Randomized Evidence.* Journal of cardiothoracic and vascular anesthesia, 2019.
9. Atalan, N., et al., *Morphine is a reasonable alternative to haloperidol in the treatment of postoperative hyperactive-type delirium after cardiac surgery.* Journal of cardiothoracic and vascular anesthesia, 2013. **27**(5): p. 933-8.
10. Subramaniam, B., et al., *Effect of Intravenous Acetaminophen vs Placebo Combined With Propofol or Dexmedetomidine on Postoperative Delirium Among Older Patients Following Cardiac Surgery: The DEXACET Randomized Clinical Trial.* JAMA, 2019. **321**(7): p. 686-696.
11. van Eijk, M.M. and A.J. Slooter, *Duration of ICU delirium, severity of the underlying disease, and mortality.* American journal of respiratory and critical care medicine, 2010. **181**(4): p. 419-20; author reply 420-1.
12. Tang, C. and Z. Xia, *Dexmedetomidine in perioperative acute pain management: a non-opioid adjuvant analgesic.* J Pain Res, 2017. **10**: p. 1899-1904.
13. Tang, C. and Z. Xia, *Dexmedetomidine in perioperative acute pain management: a non-opioid adjuvant analgesic.* Journal of pain research, 2017. **10**: p. 1899-1904.
14. Mazzeffi, M., K. Johnson, and C. Paciullo, *Ketamine in adult cardiac surgery and the cardiac surgery Intensive Care Unit: an evidence-based clinical review.* Ann Card Anaesth, 2015. **18**(2): p. 202-9.
15. Mu, J.L., A. Lee, and G.M. Joynt, *Pharmacologic agents for the prevention and treatment of delirium in patients undergoing cardiac surgery: systematic review and metaanalysis.* Crit Care Med, 2015. **43**(1): p. 194-204.

16. Shehabi, Y., et al., *Early Sedation with Dexmedetomidine in Critically Ill Patients.* The New England journal of medicine, 2019. **380**(26): p. 2506-2517.
17. Maitra, S., et al., *[Perioperative gabapentin and pregabalin in cardiac surgery: a systematic review and meta-analysis].* Revista brasileira de anestesiologia, 2017. **67**(3): p. 294-304.
18. Ucak, A., et al., *The effects of gabapentin on acute and chronic postoperative pain after coronary artery bypass graft surgery.* Journal of cardiothoracic and vascular anesthesia, 2011. **25**(5): p. 824- 9.
19. Wick, E.C., M.C. Grant, and C.L. Wu, *Postoperative Multimodal Analgesia Pain Management With Nonopioid Analgesics and Techniques: A Review.* JAMA Surg, 2017. **152**(7): p. 691-697.
20. Frenkel, C. and B.W. Urban, *Molecular actions of racemic ketamine on human CNS sodium channels.* Br J Anaesth, 1992. **69**(3): p. 292-7.
21. Gupta, A., L.A. Devi, and I. Gomes, *Potentiation of mu-opioid receptor-mediated signaling by ketamine.* J Neurochem, 2011. **119**(2): p. 294-302.
22. Cameron, M., et al., *Intraoperative Ketamine for Analgesia Post-Coronary Artery Bypass Surgery: A Randomized, Controlled, Double-Blind Clinical Trial.* Journal of cardiothoracic and vascular anesthesia, 2020. **34**(3): p. 586-591.
23. Weibel, S., et al., *Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis.* Br J Anaesth, 2016. **116**(6): p. 770-83.
24. Kranke, P., et al., *Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery.* Cochrane Database Syst Rev, 2015(7): p. CD009642.
25. Castro, J. and M.F. Cooney, *Intravenous Magnesium in the Management of Postoperative Pain.* J Perianesth Nurs, 2017. **32**(1): p. 72-76.
26. Albrecht, E., et al., *Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis.* Anaesthesia, 2013. **68**(1): p. 79-90.
27. Johnson, K.B., *Clinical Pharmacology for Anesthesiology* 2015.
28. Duan, X., et al., *Efficacy of perioperative dexmedetomidine on postoperative delirium: systematic review and meta-analysis with trial sequential analysis of randomised controlled trials.* Br J Anaesth, 2018. **121**(2): p. 384-397.
29. Markham, T., et al., *Assessment of a multimodal analgesia protocol to allow the implementation of enhanced recovery after cardiac surgery: Retrospective analysis of patient outcomes.* J Clin Anesth, 2019. **54**: p. 76-80.