

**EVALUATION OF OPIOID-FREE ANAESTHESIA IN
CURTAILING POSTOPERATIVE SERUM LEVELS OF
INFLAMMATORY MARKERS AND PROVIDING
POST-OPERATIVE ANALGESIA IN OPEN ABDOMINAL
HYSTERECTOMIES—A PROSPECTIVE COMPARATIVE
STUDY.**

BY

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BLDE (DEEMED TO BE UNIVERSITY)
VIJAYAPURA, KARNATAKA



In partial satisfaction of the criteria for attainment of the degree of.

DOCTOR OF MEDICINE IN ANAESTHESIOLOGY

Under the guidance of

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"The practice of medicine is an art, not a trade, a calling, not a business. A calling in which your heart will be exercised equally with your head." - William Osler

These words have resonated with me through my training, and I am grateful to have had the opportunity to learn and pave my way to becoming a doctor today.

Forever keeping God, almighty, first in all my endeavours, your divine providence, love, and mercy have sustained me.

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I convey my gratitude to my patients, the nursing staff, the OT technicians, and the OT staff for their kind support and earnest cooperation.

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ABBREVIATIONS

GA: General Anaesthesia
OF: Opioid Free
OS: Opioid sparing
OB: Opioid-Based
TAH: Total Abdominal Hysterectomy
CRP: C-Reactive Protein
NLR: Neutrophil Lymphocyte ratio
PLR: Platelet Lymphocyte ratio
NIBP: Non-invasive blood pressure
HR: heart rate
MAP: Mean arterial pressure
RR: Respiratory Rate
SpO₂: Percentage of oxygen saturation
ASA: American Society of Anaesthesiologists
BMI: Body Mass Index
NRS: Numeric rating scale
PONV: Postoperative nausea and vomiting
ETT: Endotracheal tube
IV: Intravenous
IM: Intramuscular
LA: Local anesthesia
mg: milligram
mcg: microgram
Mins: minutes

ABSTRACT

BACKGROUND:

AIM:

To Demonstrate the efficacy of dexmedetomidine in reducing the effects of post-operative inflammatory responses in patients receiving general anesthesia with opioids and general anesthesia without opioids but with Dexmedetomidine for open-abdominal hysterectomy.

OBJECTIVES:

- 1: To compare the serum levels of postoperative inflammatory markers in patients receiving anaesthesia by the two different anaesthetic procedures.
- 2: To compare pain score and duration of postoperative analgesia in the two groups.
- 3: To compare the incidence of postoperative nausea and vomiting.

METHODOLOGY:

- Written informed consent taken
- Nil by mouth status was confirmed.
- IV access was secured with a 20G cannula.
- Patients underwent a thorough pre-anaesthetic evaluation with a detailed history, systemic evaluation, and airway examination. The patient was given a thorough walk-through of the anaesthetic procedure to be performed and explained the numeric rating scale. A complete blood panel workup was done along with preoperative inflammatory serum markers.

RESULTS

- The perioperative inflammatory process was affected by the choice of anaesthetic agent used. This study aimed to evaluate the efficacy of Dexmedetomidine as a substitute for opioids, which are routinely used.
- When opioids were used, the postoperative inflammatory markers were found to be significantly higher as compared to preoperative values of the same.
- Results showed that there were minimum variations in the haemodynamic parameters in the opioid-free group when compared to the opioid-based group.
- In the 24-hours after surgery, patients in the opioid-free group reported lower pain scores and required lesser rescue analgesia compared to those receiving opioid, who submitted more requests for additional pain relief.
- It was also found that the MAC for inhalational agents was significantly reduced in the OF-GA group (MAC 0.6-0.4 of isoflurane).
- Several studies have found that Dexmedetomidine is a very good analgesic and a good anxiolytic agent. Studies have also found that perioperative stress, inflammatory responses, PONV, and cognitive dysfunctions were lessened when dexmedetomidine was used.

CONCLUSIONS

Intraoperative dexmedetomidine-based analgesia resulted in longer postoperative analgesia with a lesser requirement of rescue analgesia, decreased episodes of nausea and vomiting, and better control over the inflammatory markers induced by surgery.

Keywords: Inflammatory markers, surgical stress, NRS, Dexmedetomidine, Lignocaine, CRP, NLR, PLR, PONV.

TABLE OF CONTENTS

SL.NO	TITLE	PAGE NUMBER
1	INTRODUCTION	16
2	REVIEW OF LITERATURE	18
3	OPIOID FREE ANAESTHESIA	21
4	SURGICAL STRESS	30
5	INFLAMMATORY MARKERS	38
6	BASIC PHYSIOLOGY	40
7	BASIC PHARMACOLOGY	46
8	MATERIALS AND METHODS	56
9	OBSERVATION AND RESULTS	63
10	DISCUSSION	79
11	CONCLUSION	82
12	REFERENCES	83
13	ANNEXURES	
	A. ETHICAL CLEARANCE	89
	B. SAMPLE OF CONSENT FORM	90
	C. SAMPLE OF PROFORMA	96
	D. MASTER CHART	101
	E. PLAGIARISM CERTIFICATE	105

LIST OF FIGURES

SL.NO	FIGURE	PAGE NUMBER
1	Drugs involved in overdose	21
2	Paradigm in analgesia management	23
3	Method of Total Abdominal Hysterectomy	27
4	Inflammatory markers released in surgical stress	32
5	Surgical stress response	33
6	Effect of anaesthesia on surgical stress	34
7	Physiology of pain	40
8	Numeric rating scale	44
9	Physiology of Alpha-2 Adrenoceptor	47
10	Dexmedetomidine on surgical stress	49
11	Mechanism of action of Lignocaine	52

LIST OF TABLES

SL.NO	TABLE	PAGE NUMBER
1	Intravenous and Oral Opioid drugs	22
2	Risks and benefits of opioid and non-opioid analgesics	25
3	Impact of anaesthetic drugs on surgical stress	37
4	Demographic Distribution	64
5	Mean Age Distribution	65
6	Distribution of SBP between OFA & OBA	66
7	Distribution of DBP between OFA & OBA	68
8	Distribution of MAP between OFA & OBA	70
9	Distribution of Heart rate between OFA & OBA	72
10	Comparison of Inflammatory markers	74
11	Comparison of NRS between OFA & OBA	76

LIST OF GRAPHS

SL.NO	GRAPH	PAGE NUMBER
1	Comparison of Demographic variables: Age, Height & Weight	64
2	Comparison of age distribution	65
3	Comparison of SBP at varying intervals intraoperatively	67
4	Comparison of DBP at varying intervals intraoperatively	69
5	Comparison of MAP at varying intervals intraoperatively	71
6	Comparison of Heart rates at varying intervals intraoperatively	73
7 & 8	Comparison of inflammatory markers preoperatively and postoperatively	75
9	NRS complex at different interval periods	77
10	Comparison of PONV scores	78

INTRODUCTION

An inflammatory response can be triggered by a non-infectious stimulus, such as major surgery. Surgical trauma triggers multiple stress responses and exacerbates inflammation and immunosuppression during the perioperative period. These alterations encompass the secretion of stress hormones, such as catecholamines and cortisol and elevated blood glucose levels, alongside the release of inflammatory mediators, including interleukins and tumour necrosis factor- α , as well as the impairment of immune cell function, particularly CD4 T cells ⁽¹⁰⁾.

Surgical interventions can initiate systemic inflammation, leading to the release of pro-inflammatory cytokines, impairment of endothelial function, damage to the glycocalyx, activation of neutrophils, and ultimately, resulting in tissue and multi-organ dysfunction.

The increase of these circulating catabolic hormones and inflammatory cytokines can invariably affect the surgical outcome.

The use of opioids has become habitual in post-surgical pain management. However, they are known to increase the serum levels of postoperative inflammatory markers. They also cause postoperative nausea, vomiting, drowsiness, respiratory depression, urinary retention, and dependency.

Opioid-based anaesthesia is associated with a range of adverse effects, as indicated by research. These include obstructive breathing, muscle rigidity, respiratory depression, dizziness, sedation, pruritus, shivering, urinary retention, and opioid-induced bowel dysfunction, which encompasses constipation, ileus and abdominal pain. If not addressed, these issues can escalate to severe conditions such as abdominal compartment syndrome ⁽¹⁷⁾, opioid-induced hyperalgesia and development of opioid tolerance.

Opioid-free anaesthesia has been shown to enhance postoperative outcomes across various surgical environments. It minimises adverse effects on patients and pain management while maintaining stable haemodynamics, resulting in reduced stress and lower levels of cortisol elevation.

Dexmedetomidine (DEX), a highly selective α_2 -adrenoceptor agonist exhibiting sedative, anxiolytic, analgesic, and sympatholytic effects, is also known to decrease postoperative pain, nausea, opioid requirements, and delirium when used as an adjuvant in general anaesthesia. Dexmedetomidine appears to be a promising drug and an apt replacement for opioids.

This study explores the possibilities of excluding opioids from our routine anaesthesia practice without any hindrance.

REVIEW OF LITERATURE

Mohammed A Lotfy and Mohamed G Ayaad (2022) compared general anaesthesia on a total of 90 women with fentanyl (30) and without fentanyl (30) and epidural anaesthesia (30) to analyse the serum cytokine levels. They concluded that post-operative serum inflammatory levels were higher than pre-operative levels, with significantly higher levels in patients receiving opioids. The opioid-free group showed better haemodynamic control and postoperative pain scores ⁽¹⁾.

Aliah Mohammad Fahad (2022) in a study of 395 cases, investigated the association between perioperative factors and anaesthesia on the postoperative systemic inflammatory response and clinical outcomes in patients undergoing colorectal cancer surgery as noteworthy. It has been observed that there exists a proportional relationship between the stress response and the intensity of the inflammatory immune response, as well as the invasiveness and duration of the surgical procedure. Various predictive markers for systemic inflammatory response (SIR) have been identified, including the neutrophil to lymphocyte ratio (NLR), serum C-reactive protein (CRP) levels, and the Glasgow prognostic score (GPS). Furthermore, the choice of anaesthetic technique may influence the perioperative inflammatory response by modulating neutrophil activity ⁽²⁾.

Tochie JN, Bengono Bengono RS, Metogo JM, Ndikontar R (2022) et al. enrolled 36 women to demonstrate the effectiveness and safety of a modified opioid-free protocol compared to traditional general anaesthesia in gynaecological surgical procedures. The findings indicated that the OFA group experienced considerably reduced pain levels within the initial 24 hours. The CGA group had significantly more postoperative activity during the first six hours and warranted supplementary oxygen therapy ⁽³⁾.

Titon OJ, Titon JP, Silva JCD, Ferreira MO (2021) et al conducted a study on 45 patients posted for oncological surgeries They observed that there was a significant reduction in IL-12 and TNF- α levels in these patients who received opioid-free anaesthesia and concluded that exogenous opioids can affect the systemic inflammatory and immunological patterns ⁽⁴⁾.

Soffin EM, Wetmore DS, Beckman JD, Sheha ED (2019) et al. A total of 36 patients who underwent lumbar surgery as part of their Enhanced Recovery after Surgery (ERAS) protocol for spinal decompression were included in the study to evaluate postoperative pain levels, opioid usage, and duration of stay in the Post-Anaesthesia Care Unit (PACU). The researchers determined that patients in the OFA group exhibited a notable decrease in opioid usage when compared to those in the OCA group. The study reveals an opportunity to minimise perioperative opioid consumption and provide good exposure to reinforce ERAS in the postoperative phase ⁽⁵⁾.

Siekman, W., Eintrei, C., Magnuson, A., and Sjölander (2017) conducted a study to elucidate whether perioperative epidural analgesia prevents the inflammatory response following colorectal cancer surgery. A total of 96 patients were randomized into epidural analgesia (P) or patient-controlled analgesia (E), and serum cytokines and tumor necrosis factor were studied preoperatively and postoperatively. A mixed-method analysis revealed that there were no notable differences in serum cytokine concentration between groups P and E. The research concluded that open surgery exerts a greater influence on inflammatory mediators compared to laparoscopic surgery accompanied by either epidural or intravenous analgesia ⁽⁶⁾.

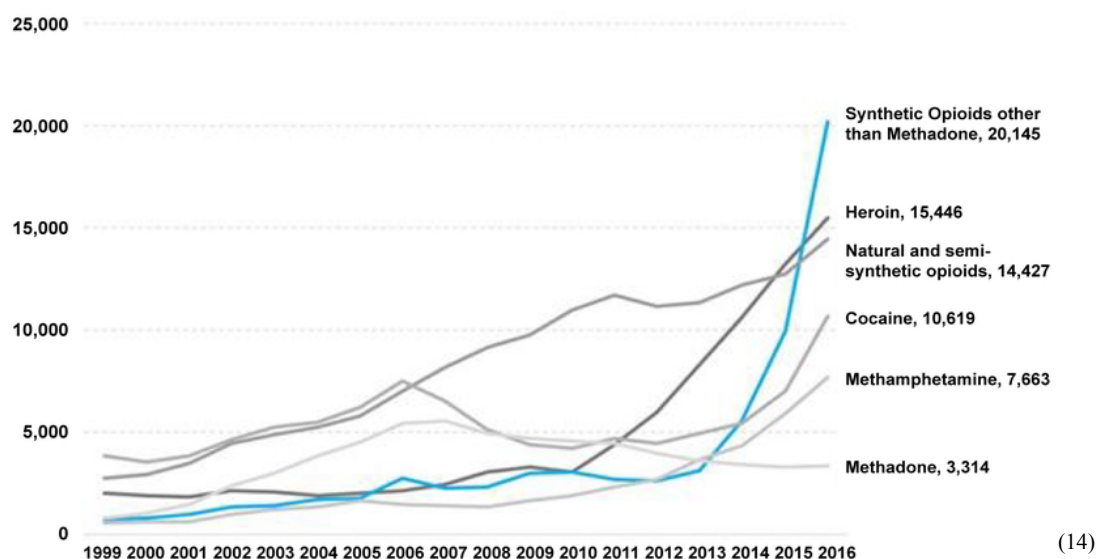
Bakan M, Umutoglu T, Topuz U, Uysal H, Bayram M, et al. (2014) hypothesised in a research study involving 80 patients who were set to undergo elective laparoscopic cholecystectomy, participants were randomly divided into two groups. One group was given opioid-based anaesthesia that included remifentanyl and propofol infusions, whereas the other group received opioid-free anaesthesia that included dexmedetomidine, lidocaine and propofol infusions. They concluded that postoperative pain, need for rescue analgesia, nausea, and vomiting were relatively lesser in the opioid-free group and it has been indicated that an opioid-free anaesthesia approach utilising dexmedetomidine, lidocaine, and propofol infusions could serve as a viable alternative technique for laparoscopic cholecystectomy ⁽⁷⁾.

OPIOID-FREE ANESTHESIA

There has been a push to limit the usage of opioids during the perioperative period owing to the steep rise in the opioid crisis. The widespread need for pain management led to a surge in opioid prescriptions, causing an opioid epidemic, leading to several deaths due to opioid overdose. This prompted the medical community to re-evaluate pain management strategies, choosing alternatives to opioid use ⁽¹²⁾.

The practice known as “opioid-free anaesthesia,” or OFA, forbids the use of intraoperative systemic, neuraxial, or intracavitary opioids. Opioid-sparing anaesthesia uses minimum quantities of opioids intraoperatively; it is a comparable but less restrictive approach and can be used as a multimodal regimen.

Drugs Involved in U.S. Overdose Deaths, 2000 to 2016



[Figure 1: Drugs involved in overdose]

The use of opioids during the perioperative phase is linked to delirium, pruritus, urine retention, respiratory depression, decreased gastrointestinal function, postoperative nausea and vomiting, and a risk of opioid addiction ⁽¹⁴⁾. Growing evidence suggests that using opioids during surgery may result in postoperative hyperalgesia, leading to long-term opioid usage and chronic postsurgical pain (CPSP).

The use of benzodiazepines and selective serotonin reuptake inhibitors (SSRIs) during the perioperative period, along with factors such as diabetes, younger age, lower income, increased intraoperative opioid administration, and the length of acute postoperative opioid consumption, is recognised as a contributor to a heightened risk of extended postoperative opioid use ⁽¹⁵⁾.

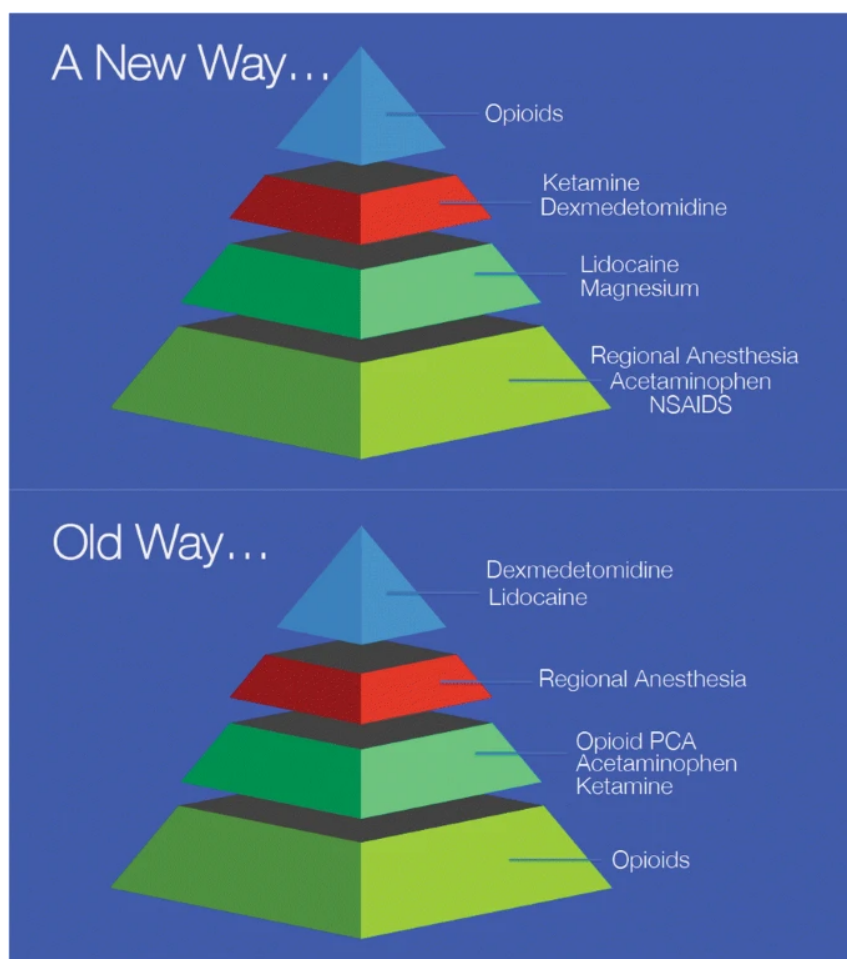
Public education efforts are currently in progress to teach addicts' family members how to prevent opioid-induced respiratory depression. Preventing the onset of addiction, particularly in relation to surgical admissions, will be a more effective approach to primary prevention of opioid addiction.

The frequently utilised arsenal of non-opioid analgesics comprises of local anaesthetics, clonidine, dexmedetomidine, ketamine, gabapentin, magnesium sulfate, and dexamethasone ⁽¹²⁾.

Drug	Dosage
IV Dexmedetomidine	0.25 mcg/kg boluses (0.5-mcg/kg/hr infusion)
IV Acetaminophen	15 mg/kg every 6 hours
IV Ketorolac	30 mg every 6 hours
IV Ketamine	0.25 mg/kg boluses (0.1 mg/kg/hr infusion)
IV Lidocaine	1 mg/kg loading dose (1-2 mg/kg/hr infusion)
Oral Gabapentin	300 mg PO daily
Oral Pregabalin	150 mg PO daily
IV Magnesium	30 mg/kg loading dose (10 mg/kg/hr infusion)

Table 1: Intravenous and Oral Opioid Replacement Drugs

The related side effects guide and limit the use of these medications, although many of them have demonstrated satisfactory effectiveness in sustaining antinociception. However, these medications can produce the intended effects when taken in sub-anaesthetic dosages or as an OSA adjunct. These medications are not new to clinical pharmacology, but their functions have been modified for secure and efficient drug delivery systems.



[Figure 2: New paradigm in analgesia management ⁽¹⁵⁾]

One viable option to incorporate opioid-sparing or opioid-free regimens into clinical practice is through ERAS pathways ⁽¹³⁾. The collaboration of the anaesthesia, surgical, and nursing teams is the fundamental ERP principle to achieve the goal of delivering optimal analgesia.

Optimal analgesia can be defined as “a technique that optimises patient comfort and facilitates recovery of physical function while minimising the adverse effects of analgesics⁽¹⁵⁾”.

These treatments' underpinnings are based on multimodal nonopioid analgesic regimens. As long as there are no contraindications, these regimens usually start with a combination of acetaminophen, an NSAID, and a gabapentinoid during the preoperative phase.

Following this, regional anaesthetic techniques are used intraoperatively where appropriate, and a multimodal analgesic pain regimen is continued into the postoperative phase with scheduled gabapentinoids, NSAIDs, and acetaminophen. The multimodal pain pathway is subsequently completed by managing breakthrough pain with the prudent use of opioid analgesics.

It is premature to think that opioids can be removed from the practice of anaesthesia, particularly since they are the main medication used for PCA. Their quick onset and consistent duration offer a clear advantage over OFA. Reducing the usage of opioids and guaranteeing adequate pain relief using multimodal pain management strategies should be the ideal pain treatment goals to maximise patient benefit⁽¹²⁾.

Effective OFA administration and monitoring have a learning curve. The usage of various medications in the OFA regimen, their indication in particular procedures, and the best time to provide them all need further research.

The time has come to shift the foundation of our practice from an opioid-based approach to a multimodal approach. In which non-opioid-based agents are used to manage analgesia first, followed by additional layers of analgesics, with opioids remaining the cornerstone of analgesics.

As we enter a new era of anaesthesia, we must improve patient recovery after surgery by reducing postoperative and postanesthetic side effects in addition to using better surgical techniques.

Table 2: Risks and benefits of opioid and non-opioid analgesics ⁽¹⁴⁾

	Opioid Analgesia	Opioid free/ Opioid Sparing Analgesia
Risks	Respiratory depression Need for post-op ventilation with ventilator-associated pneumonia Addiction Nausea & Vomiting Gastrointestinal dysfunction, ileus Pruritus Urinary retention	Bradycardia with dexmedetomidine Hepatic damage with acetaminophen Bleeding, renal impairment and bronchospasm with ketorolac Hallucinations, tachycardia and addiction with ketamine Tinnitus, seizures and cardiac arrest with lidocaine Sedation with gabapentin Hypotension with magnesium
Benefits	Analgesia Ready acceptance of poor patient outcomes by peers, due to the conventional nature of the analgesic therapy	No respiratory depression No addiction except for ketamine Less need for post-OP ventilation No nausea and vomiting No gastrointestinal dysfunction and ileus No pruritus No urinary retention

Dexmedetomidine and Lignocaine for OFA

Dexmedetomidine and lignocaine have a lower risk of opioid-related perioperative problems by having an analgesic effect without producing severe respiratory depression and opioid-sparing effects.

Dexmedetomidine is a wonder drug in the world of opioid-free anaesthesia. Being a selective alpha-2 adrenergic agonist, it acts directly on spinal preganglionic sympathetic neurones to suppress sympathetic nervous system activity. It is frequently used for analgesia, sedation and anxiolysis to lessen the need for anaesthetics during general anaesthesia. It has replaced perioperative opioid utilisation to a large extent. Dexmedetomidine 0.1 to 1.0 µg/kg is slowly administered over 10 minutes.

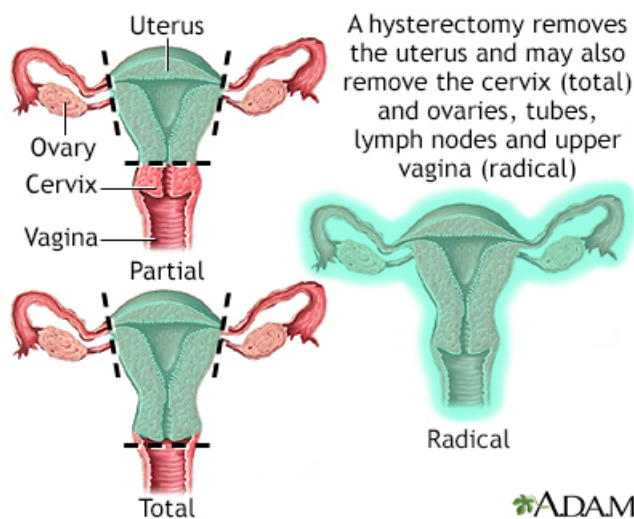
Lignocaine possesses coanaesthesia effects and has been shown to provide analgesia, anti-inflammatory and immunomodulatory properties that help decrease postoperative ileus, nausea and vomiting and speed up the recovery of bowel function and hospital stay. It is believed that lignocaine's antinociceptive action is mostly due to the downregulation of neutrophil degranulation, not merely its ability to block sodium channels. Lignocaine 1.5 mg/kg is slowly administered over 10 minutes.

Both lignocaine and dexmedetomidine have shown promising effects and methods in bringing about opioid-sparing effects and advantages for opioid-free anaesthesia.

ABDOMINAL HYSTERECTOMY

Hysterectomies are one of the most common procedures performed worldwide. It is the surgical removal of the uterus through an incision in the lower abdomen along with the removal of one or both ovaries and fallopian tubes. An abdominal hysterectomy is usually recommended for several conditions, such as abnormal uterine bleeding, fibroids, pelvic organ prolapse, endometrial hyperplasia, and other cervical abnormalities.

Figure 3 : Method of TAH



ADAM. _ Premenopausal women decide to keep their ovaries for regulation of hormones to help reduce the risk of heart diseases and prevent or reduce menopausal symptoms. Whereas postmenopausal women benefit from the removal of ovaries, reducing the risk of developing ovarian cancer.

The technique and route of delivery of the uterus depend on a combination of factors, including anticipated pathology, patient habitus, concurrent abdominal and vaginal procedures, and the expertise of the surgeon.

The purpose of anaesthesia in total abdominal hysterectomies is to provide adequate pain management to decrease postoperative morbidity, reduce length of hospital stay, and reduce chronic pain.

The majority of studies evaluating the quality of postanesthetic and surgical recovery typically look at factors such as length of stay, pain, recovery time, cardiorespiratory problems, and postoperative nausea and vomiting. When considered separately, these factors may not accurately reflect how most patients recover from anaesthesia and surgery. Thus, quality of life evaluation from the perspective of the patient has emerged as a crucial element to take into account in research examining the impact of anaesthesia and surgery on patient satisfaction and recovery ⁽²¹⁾.

Spinal anaesthesia has evolved as the gold standard approach for treatments in obstetrics and gynaecology. However, the most popular technique for abdominal hysterectomy is still general anaesthesia, as previous research has not demonstrated any benefits from neuraxial block ⁽¹⁸⁾.

After an abdominal hysterectomy, the choice of anaesthetic plan is frequently left to the preference of surgeons and anaesthesiologists due to the absence of positive recovery outcomes when comparing anaesthetic approaches ⁽¹⁹⁾. Even though neuraxial anaesthesia is an option, it can be time-consuming and has a higher failure rate.

The primary objective of this study was to compare the effect of general anaesthesia with and without the usage of opioids. To understand the quality of postoperative recovery, pain management, and postoperative nausea and vomiting. Curating a method in opioid-free anaesthesia with minimal effects on patient outcomes.

Preoperatively

- Repeated information concerning pre-, per-, and postoperative care.
- Paracetamol orally one hour before surgery.
- Clear fluids orally until two hours before surgery.
- Acupressure wrist bands applied and maintained through hospital stay.
- Antibiotic and antithrombotic prophylaxes.



Peroperatively

- SA with hyperbaric bupivacaine 20 mg and morphine 0.2 mg intrathecally. Sedation with intravenous propofol.
- GA with propofol, fentanyl and rocuronium. 5 mg morphine given intravenously 20 minutes before ending the operation. Orogastric tube during surgery.
- Parenteral fluid regulation aimed at 25 mL/kg/day.
- Bupivacaine injected in abdominal wall wound.
- Transurethral catheter inserted preoperatively and left until next morning.



Postoperatively

- In PACU pain management initiated orally with paracetamol and NSAID. Patient permitted to drink and mobilization encouraged. Rescue antiemetic given when needed. Discharged to gynecological ward when vital signs stable.
- Inward continuous monitoring, pain and PONV management. Opioids avoided if possible. Early nutrition and mobilization actively encouraged. Standardized criteria of discharge.
- After discharge from hospital, pain management given orally with paracetamol and NSAID. Duration of use of analgesics decided on by the patient.

SURGICAL STRESS

All metabolic and hormonal alterations caused by a traumatic experience at the micro- and macrocellular levels are included in the human physiological response “to stress.”

Surgical trauma, especially the kind that results from major procedures, causes deep physiologic changes that affect the immune system, metabolism, and inflammation. These changes affect how the body’s organs function on a broad scale⁽¹⁶⁾.

The stress reaction to surgery is a typical term used to describe this total effect. Many researchers have tried to determine how to assess the stress response to surgery because the degree of stress response is approximately proportional to the severity of the surgery and affects the postoperative problems as well as the patients convalescence and morbidity.

The stress response to tissue injury is of the following phases: the first “EBB phase,” the second “flow phase,” and the third “recovery phase.”.

In order to preserve physiological homeostasis during the perioperative period, surgical trauma activates the nociceptors of the somatosensory nervous system as well as immune cells. This results in surgical stress responses, which include the hypothalamic-pituitary-adrenal axis, sympathetic nervous systems, and immune responses ⁽²²⁾.

Numerous organs receive and transmit signals from the central nervous system, which affects how they function. The sympatho-adrenomedullary axis (SAM) and the hypothalamic-pituitary-adrenal axis (HPA) get activated through surgical trauma. The SAM axis triggers nociception by activating peripheral pain receptors through unpleasant mechanical pressure stimuli ⁽³⁵⁾. Myelinated A δ fibres and unmyelinated C fibres carry information to the cerebral cortex and thalamus when the sympathetic nervous system is triggered.

When the SAM axis is triggered, acetylcholine neurotransmitters are released, stimulating the adrenal gland to create norepinephrine and epinephrine there, causing tachycardia and hypertension. The cardiovascular, renal and pulmonary systems are all impacted by RAA overactivation, and fluid retention and oliguria are frequently observed in the postoperative phase ⁽³⁵⁾.

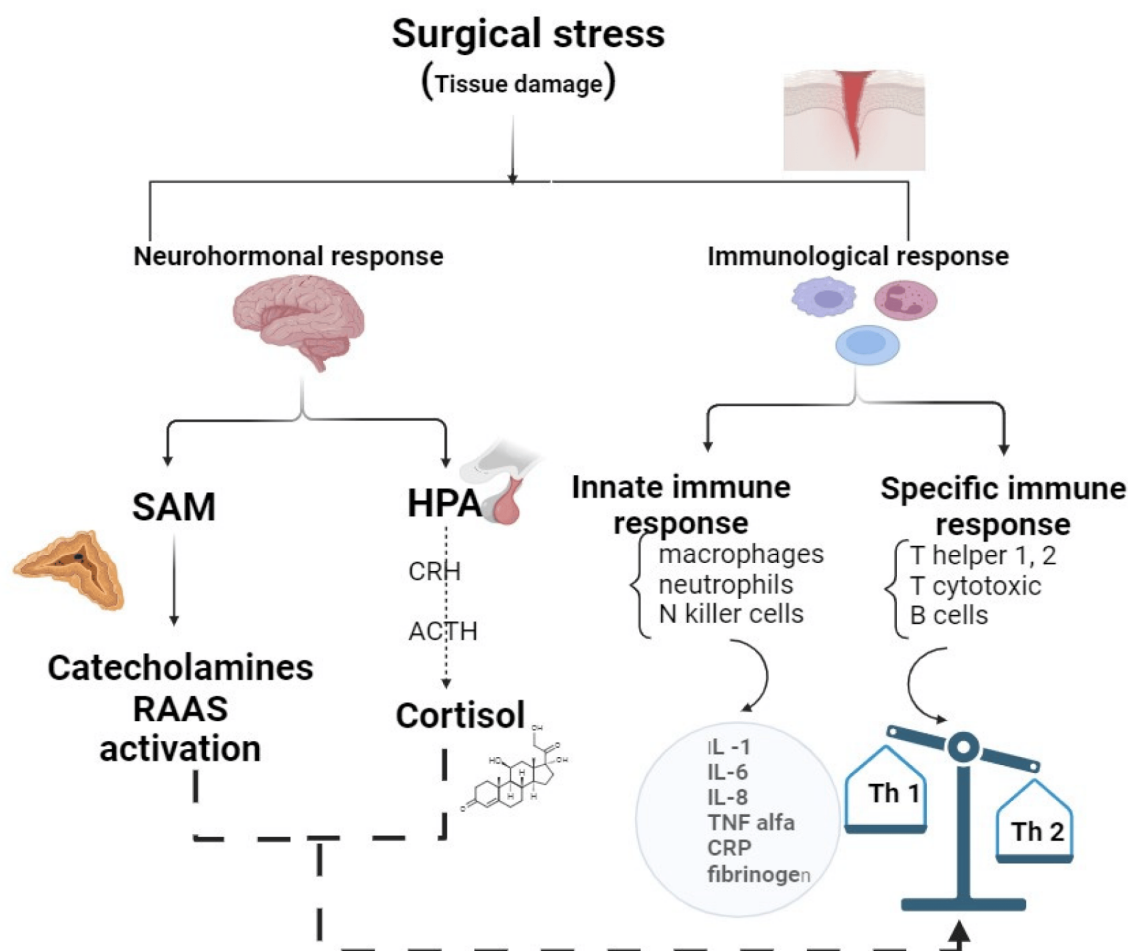
Significant alterations include the release of inflammatory mediators such as interleukins, tumour necrosis factor- α , stress hormones (such as catecholamine, cortisol, and blood glucose), and immune cell dysfunction (such as CD4 β T cells) ⁽¹⁰⁾. These can all lead to a higher risk of postoperative infection, delayed wound healing, multiple organ dysfunction, and an increased risk of morbidity and mortality.

Interleukins and tumour necrosis factor- α are identified as biomarkers of surgical stress. IL-10 acts as an anti-inflammatory interleukin that prevents the production of proinflammatory cytokines. Tumour necrosis factor α is proinflammatory and starts an acute phase reaction with local and systemic inflammation.

Measuring the plasma levels of certain proteins and enzymes linked to tissue damage, such as creatinine phosphokinase (CPK), C-reactive protein (CRP), lactic dehydrogenase (LDH), cancer antigen 125 (CA-125), tumour necrosis factor- α (TNF- α), and interleukin 6 (IL-6), can help determine the extent of surgical trauma ⁽¹⁶⁾. Lymphocytes, monocytes, neutrophils and platelets have also been used to predict the prognosis of disease and the course of inflammation, i.e., NLR (neutrophil-lymphocyte ratio), PLR (platelet-lymphocyte ratio), and MPV (mean platelet volume) ⁽⁴⁶⁾.

The inflammatory response and surgical outcomes that arise from surgical trauma may be modulated by the chosen anaesthesia technique.

[Figure 4: Inflammatory markers released in surgical stress]

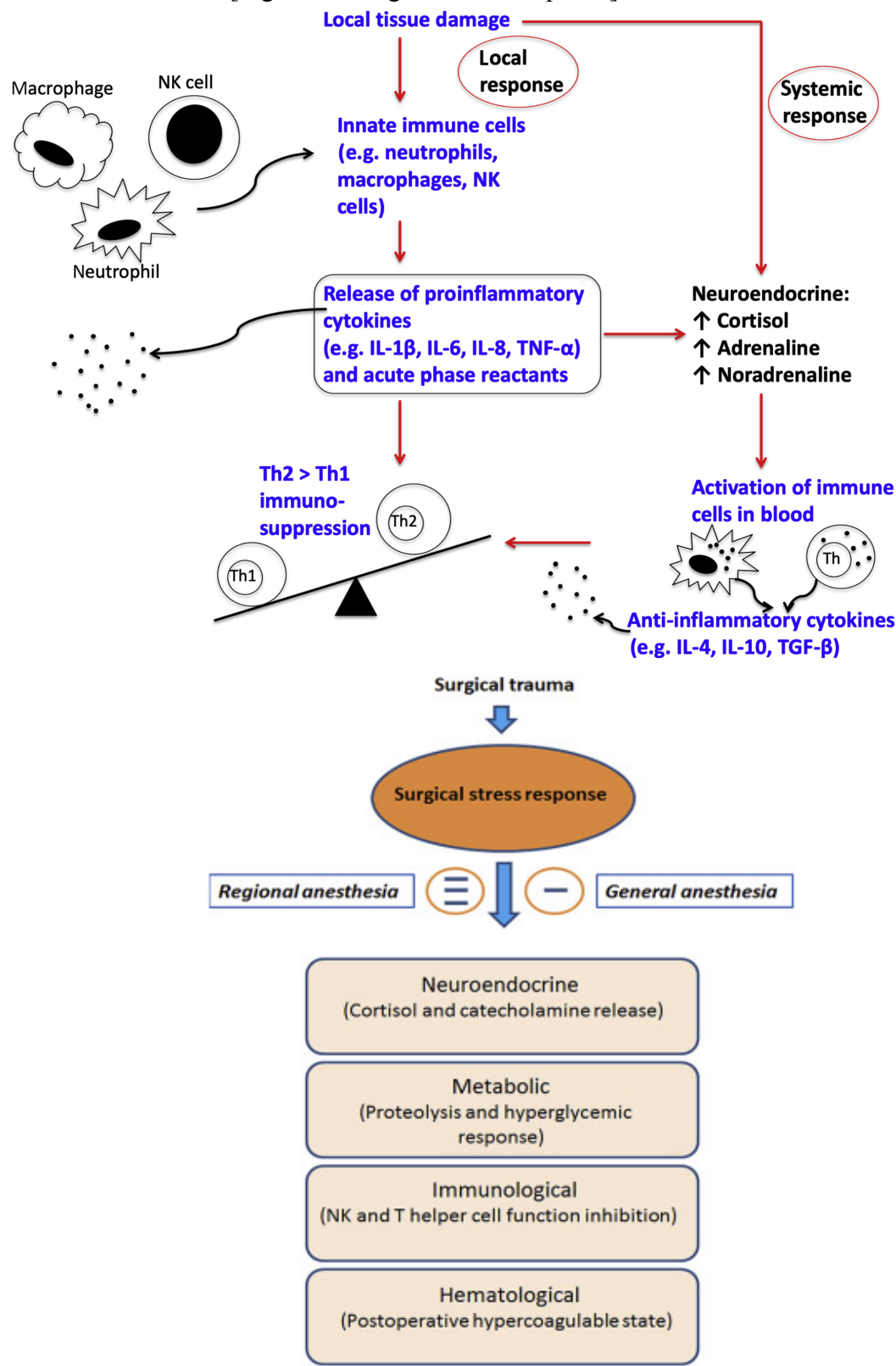


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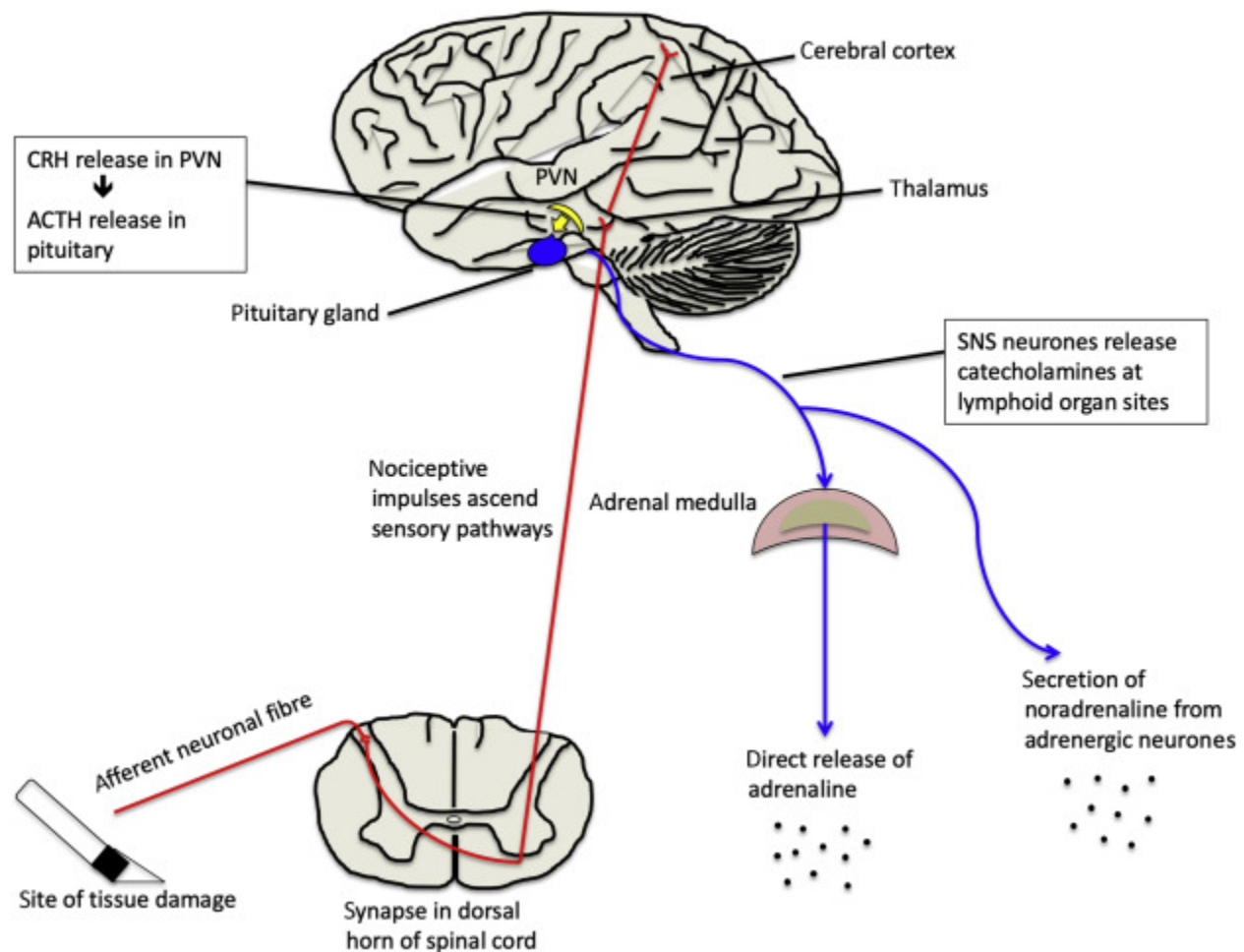
The invasiveness and length of the operation affect the extent of these integrated responses. A physiological and pathological reaction to surgical trauma, the surgical stress response includes both inflammatory-immune and neuroendocrine metabolic reactions.

Therefore, in order to potentially reduce postoperative problems and enhance clinical outcomes, it is imperative to put methods in place during the perioperative period to manage surgical stress, inflammation, and immunity.

[Figure 5: Surgical stress response]



THE EFFECT OF ANAESTHESIA ON SURGICAL STRESS



[Figure 6: Effect of anaesthesia on surgical stress]

In order to ensure analgesia, hypnosis, muscle relaxation, and the homeostasis of the perioperative body, anaesthesia makes surgery possible. The surgical stress response can be influenced by both the anaesthetic method and the anaesthetic medications used.

Because of the possible positive impact on surgical results, there has been a lot of interest in altering the stress response. The selection of the analgesic methods employed determines how much the reactions are altered.

Anaesthetic drugs and techniques play a crucial role in modulating the surgical stress response. From the preoperative phase, the surgical stress response can be reduced, lessening the burden of surgical trauma by prolonged hunger avoidance, beta-blocker use, anxiolytics, and reassurance.

At the hypothalamic-pituitary level of the HPA axis, benzodiazepines such as midazolam 0.2-0.4 mg/kg or an infusion at 0.9 to 0.125 mg/kg/hr suppress the synthesis of cortisol. There have been reports of this effect in both abdominal and limb procedures.

Propofol's single induction dose of 1-2 mg decreases circulating cortisol concentrations; however, it does not totally stop cortisol and aldosterone secretion. Cortisol secretion may be totally stopped by a continuous infusion of propofol with a plasma concentration of 4–8 mcg/ml ⁽³⁵⁾.

By lowering CRH release at the hypothalamus level, systemic opioids decrease the secretion of ACTH and GH. High doses of opioids completely suppress both ACTH and cortisol. However, this dose level would greatly prolong re-emergence from anaesthesia and is related to a demand for postoperative ventilatory assistance. Systemic opioids may decrease the hyperglycaemic reaction to surgery.

Large doses of morphine suppress growth hormone and inhibit cortisol release. Fentanyl, sufentanil, and alfentanil suppress pituitary hormone secretion. It has been noticed that fentanyl 50 mcg/kg decreases growth hormone, cortisol, and glycaemic levels in lower abdominal surgeries.

Opioids have immunomodulatory effects; an explanation for this could be that opioids that can cross the blood-brain barrier have a higher immunomodulatory impact than those that cannot.

During surgery, the stress response is changed both by intravenous and inhalational anaesthesia. Compared to intravenous anaesthetics like propofol and remifentanyl, volatile anaesthetics reduce cortisol, ACTH, growth hormone, and catecholamines more when a surgical insult occurs ⁽³⁴⁾.

The complicated and poorly understood relationship between opioids, it dependence, and cancer has led to a growing interest in developing opioid-free anaesthesia methods ⁽³⁴⁾.

For integrated pain management. Opioid-sparing solutions have surfaced, utilising non-opioid analgesics, anti-hyperalgesics, and loco-regional approaches. A combination of intravenous dexmedetomidine, ketamine, and lignocaine is being used with newer additions such as magnesium sulphate, gabapentin, dexamethasone, paracetamol, and NSAIDs.

Modifying the neuroinflammatory immune stress response, improving recovery, lowering prescription misuse, abuse, addiction, tolerance, and hyperalgesia, preventing sensitisation, preventing chronic postsurgical pain, and allowing for an early hospital discharge are all the advantages of opioid-free/opioid-sparing techniques in anaesthesia practice.

Because of the possible positive impact on surgical results, there has been a lot of interest in altering the stress response. The selection of the analgesic methods employed determines how much the reactions are altered ⁽³⁶⁾.

The ESPEN guidelines on clinical feeding in surgery advise early postoperative enteral feeding, oral carbohydrate administration the night before and two hours before surgery, and brief preoperative fasting to minimise stress-related catabolism.

By employing appropriate general anaesthetics, managing intraoperative fluid, and preventing intraoperative haemodynamic variations, we can control surgical stress intraoperatively. Multimodal analgesia, early mobilisation, and early enteral nutrition in the postoperative period are essential in decreasing stress response and easing patient recovery.

Anaesthetic drugs and their impact on surgical stress response.

Drug	Implications
Volatile anesthetics	Suppress cortisol, ACTH, GH, and catecholamine. Cardioprotective effects Decrease NK cell cytotoxicity. Possible negative effects on cancer progression
Propofol	Inhibits the sympathetic nervous system Decreases HIF1 α and induces anti-inflammatory and anti-oxidant effects Potential beneficial effect on Th1/Th2 ratio and preserves the function of natural killer cells Propofol-TIVA seems to decrease mortality and cancer recurrence
Etomidate	Suppresses adrenal cortisol secretion Continuous infusion associated with increased mortality in critically ill patients
Ketamine	Decreases NK cell activity
Opioids	Reduces CRH, ACTH, and cortisol secretion Immunosuppressive effects impairing monocyte and neutrophil function, NK cell-mediated cytotoxicity, and lymphocyte and macrophage proliferation Possible association with tumor recurrence after cancer surgery
Dexmedetomidine	Inhibitory effects on the release of epinephrine, norepinephrine, and cortisol Decreases IL-6, TNF- α , CRP, increases IL-10, the CD4 $^{+}$:CD8 $^{+}$ ratio, and the Th1:Th2 ratio
Intravenous lidocaine	Reduces inflammation and has possible antineoplastic effects

Table 3: Impact of anaesthetic drugs on surgical stress

INFLAMMATORY MARKERS

CRP

A member of the pentraxin family of proteins CRP is a highly conserved molecule that is secreted from the liver in response to various inflammatory cytokines, primarily IL-6. CRP rises sharply in response to trauma, inflammation, and infection and swiftly returns to normal levels as the condition resolves ⁽¹⁶⁾. Hence, CRP monitoring could be used to track the extent of surgical damage.

IL-6

One cytokine involved in both innate and adaptive immune responses is interleukin-6. Monocytes, endothelial cells, fibroblasts and other cell types produce it in reaction to pathogens, but other cytokines, particularly interleukin-1 and TNF- α , can also promote it.

IL-6 plays a role in the metabolic regulation of CRP and is engaged in a number of immunological processes, including the liver's manufacture of acute phase chemicals. During an inflammatory response, both IL-6 and its receptor are highly expressed and can have unfavourable effects on a number of organs. Normally, IL-6 expression is modest, with the exception of illnesses, trauma, and the presence of stressing factors.

NLR and PLR

Platelets, neutrophils and lymphocytes are essential for controlling inflammation. Changes in the number and makeup of blood cells, such as a rise in neutrophils or a fall in lymphocytes and an increase in platelet counts, are associated with systemic inflammation ⁽⁴⁶⁾.

An affordable, straightforward, quick and readily available metric with high sensitivity and low specificity for stress and inflammation is the neutrophil-lymphocyte ratio. Dynamic changes in NLR take place hours before the clinical scenario and can notify the physician early on the ongoing pathogenic changes. Hence, it is efficiently used in ICU, surgery and oncology.

Platelet lymphocyte ratio and mean platelet volume can also be used to assess inflammation. Neutrophil, lymphocyte and monocyte values are taken from complete blood count and used to calculate NLR and PLR.

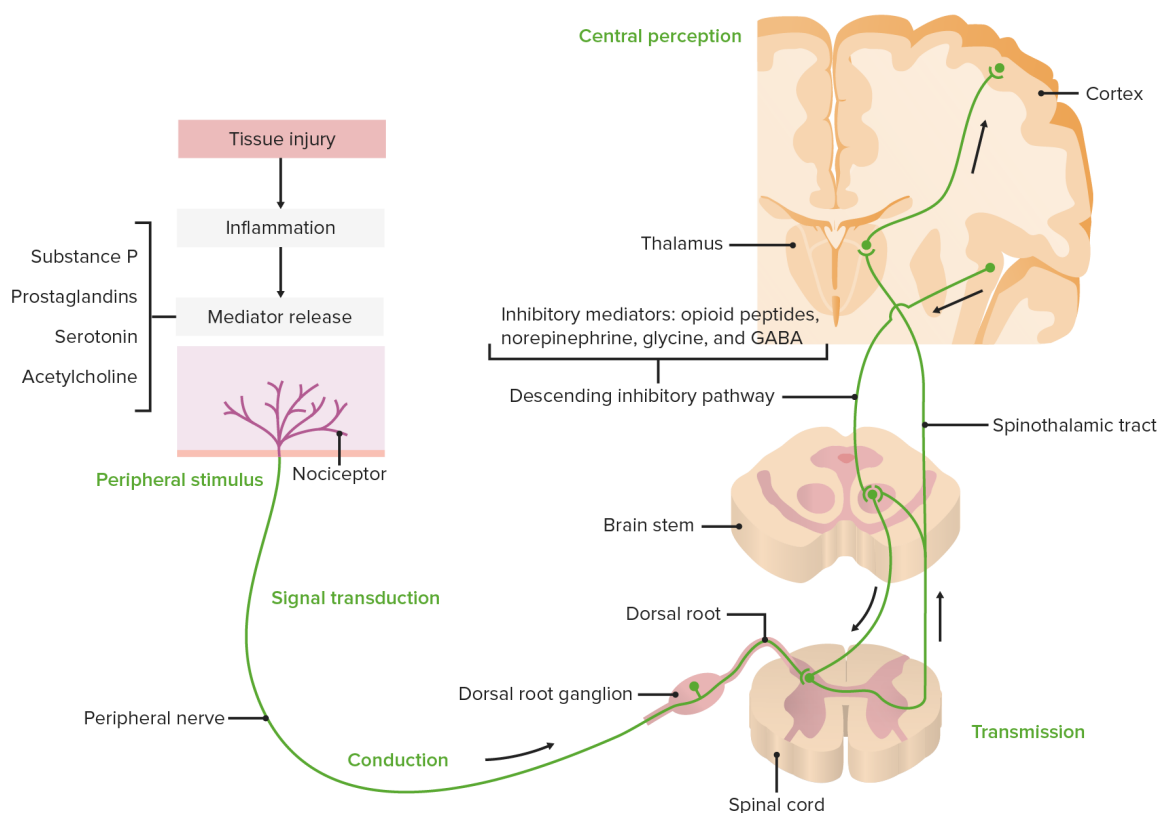
The dynamic interaction between innate (neutrophils) and adaptive (lymphocytes) cellular responses during various disease conditions is reflected by NLR and PLR.

It has been demonstrated that polymorphonuclear leukocytes, as well as macrophage and monocyte activities, are directly impacted by the anti-inflammatory qualities of local anaesthesia.

Since the local release of proinflammatory mediators also causes peripheral sensitisation, which subsequently intensifies pain perception, pain and inflammation are tightly related. Inflammation and onset of pain are related according to studies.

PHYSIOLOGY OF PAIN

The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”. This concept acknowledges the interaction between pain's subjective, emotional, and psychological elements as well as its objective, physiological sensory features.



[Figure 7: Physiology of pain]

Pain consists of three distinct dimensions: the sensory-discriminative aspect, which pertains to the location and intensity of the pain; the motivational-affective component, which encompasses feelings such as depression and anxiety; and the cognitive-evaluative dimension, which involves thoughts regarding the cause and significance of the pain. It is important to note that pain is inherently subjective, making it impossible to measure objectively.

Pain is transmitted through three neuronal pathways that carry harmful stimuli from the periphery to the cerebral cortex.

Pain Transmission ⁽²³⁾:

- Transduction: Nociceptors convert painful stimuli into electrical signals; it is a process by which tissue-damaging stimuli activate nerve endings.
- Transmission: electrical signals travel through A-delta and C-fibres for the spinal cord. This pertains to a series of functions through which the message is transmitted from the site of tissue injury to the perception-related parts of the brain.
- Modulation: Is a neural mechanism that specifically serves to diminish activity within the transmission system. Modulated by various neurotransmitters and receptors in the spinal cord.
- Perception: subjective awareness produced by sensory signals. It is a multifaceted operation involving various processes of focus, anticipation, and understanding.

Pain Processing

Signals are initially processed in the dorsal horn of the spinal cord before being relayed to the brainstem. At this stage, they undergo additional processing before ultimately reaching the cerebral cortex, where they are perceived and interpreted.

Pain modulation

- Descending inhibition: the brain sends a signal to the spinal cord to inhibit pain transmission.
- Ascending facilitation: the spinal cord sends signals to the brain to facilitate pain transmission
- Neurotransmitters such as endorphins, opioids, and serotonin modulate pain transmission.

Pain perception

Signals are transmitted from the brainstem to the thalamus, which then relays them to the cerebral cortex, where pain is perceived.

There are three types of acute postoperative pain: neuropathic, inflammatory, and nociceptive. Thinly myelinated A-delta fibres, myelinated A-beta fibres, and activated unmyelinated C-fibres all play a role in nociceptive pain. This kind of pain typically results from unpleasant stimuli like direct intraoperative tissue damage, i.e., making a skin incision ⁽²⁵⁾.

When inflammatory mediators like cytokines are released, nociceptive fibres become sensitised, resulting in inflammatory pain. The four traditional indicators of inflammation—pain, heat, erythema, and swelling—may be included in the clinical presentation of inflammatory pain. Inflammatory discomfort is usually curable and can last for hours to days. Increased axonal sensitivity to stimuli causes neuropathic pain, caused by damage to neuronal structures. In the initial postoperative period, neuropathic pain will manifest and could develop into persistent postoperative pain ⁽²⁵⁾.

In the context of opioid-free anaesthesia, we implement standard monitoring of patient vital signs as a compulsory practice in accordance with established clinical guidelines.

This encompasses the use of a pulse oximeter, electrocardiogram, blood pressure monitor, temperature probe, oxygen analyser, and carbon dioxide analyser, in addition to respiratory parameters on the anaesthesia machine. We also utilise bispectral index monitoring to guarantee adequate levels of hypnosis, along with train of four monitoring to verify the effectiveness of muscle blockade ⁽¹⁷⁾.

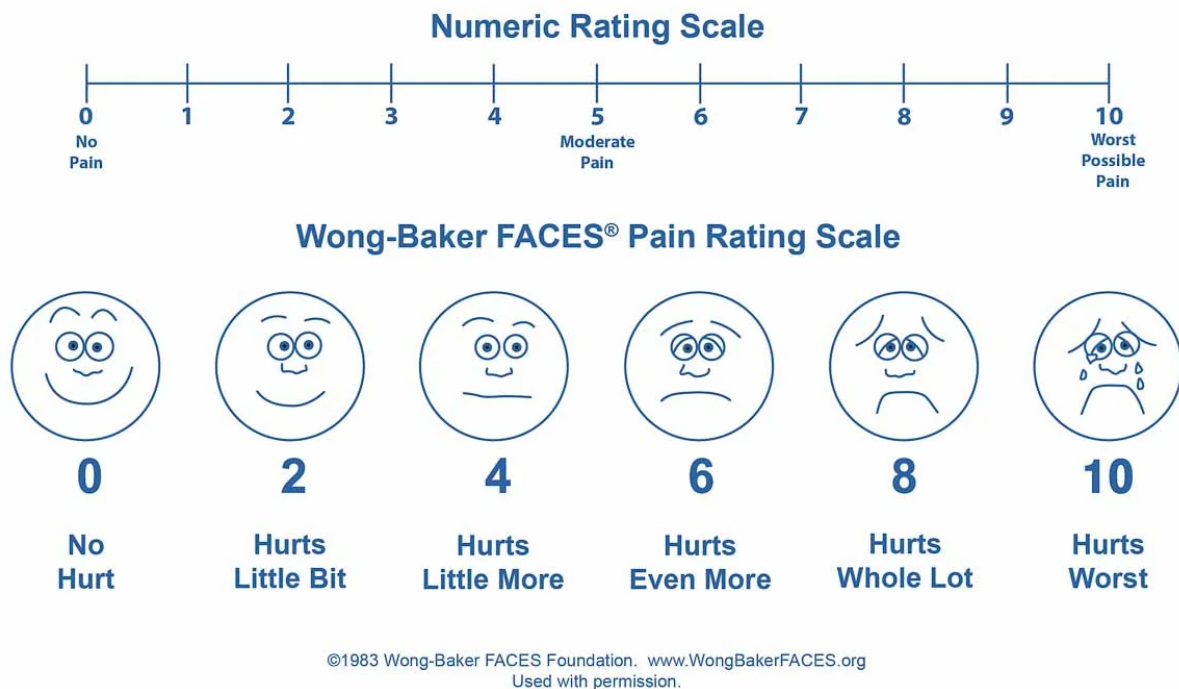
The challenge pertains to the validation of pain during surgical procedures. While pain is acknowledged as the fifth vital sign, there is presently no reliable instrument available that can effectively evaluate intraoperative analgesia and anti-nociception, aside from the previously mentioned circulatory indicators such as blood pressure and heart rate.

By increasing catecholamine and cortisol levels, pain can change a patient's endocrine response. It can also strengthen autonomic reflexes, resulting in vagal syndromes or hypertensive crises, which can have serious consequences both before and after surgery. Additionally, elevated levels of postoperative pain can adversely affect various "soft" outcomes, such as restrictions in physical function, sleep quality, and psychological well-being ⁽¹⁸⁾.

The objective of managing postoperative pain is to lessen the impact of pain following surgery and facilitate patients' return to their usual activities. Recent developments highlight the importance of a multimodal analgesic strategy that is customised to each patient's comorbid conditions and social circumstances. This approach is associated with a decrease in opioid use after surgery, shorter hospital stays, reduced perioperative anxiety, and fewer requests for sedative medications ⁽²⁵⁾.

PAIN ASSESSMENT

Numeric rating scale:



[Figure 8: Numeric rating scale]

An unidimensional indicator of adult pain intensity is the numeric pain rating scale (NPRS). The visual analogue scale is represented by this segmented numeric rendition, which spans a range of 0 to 10.

The 11-point numeric rating scale ranges from ‘0’ indicating one pain extreme, i.e., zero/no pain, to ‘10,’ indicating the other pain extreme, i.e., severe/worse pain imaginable ⁽²⁴⁾.

Patients are asked to encircle the number that corresponds to the level of pain they are experiencing at the moment in order to graphically display the NRS. The verbal

numeric scale (VNS) is a variant of this scale in which patients are asked to express vocally the degree and severity of their pain.

Advantages:

- Easy to understand and administer
- Quick and convenient
- Sensitive to changes in pain intensity

Limitations:

- Subjective and relies on patients self-report
- May not be suitable for patients with language barriers, cognitive impairments, and cultural differences.

Implementation considerations:

- Timing: assess pain regularly, ideally at fixed intervals.
- Documentation: record NRS in patients records to track progress and guide care decisions.
- Multimodal pain management: NRS can be used to assess and adjust pain management strategies, including pharmacological and non-pharmacological interventions.



MEDICALNEWS TODAY



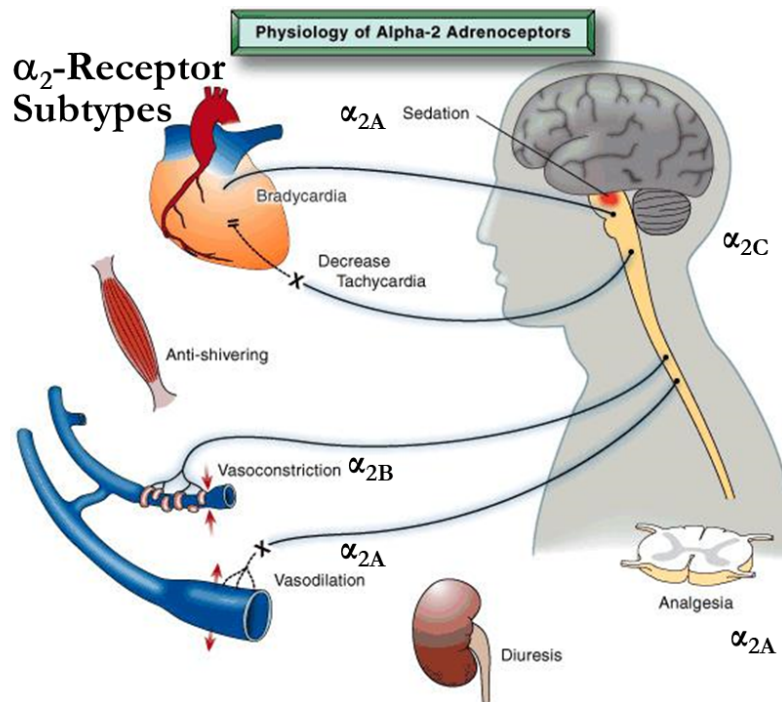
Generic name:	Dexmedetomidine
Brand name:	Precedex, Dexmed
Metabolism:	near-complete hepatic metabolism
Elimination:	2-4 hours
Onset of action:	15 minutes from administration
Bioavailability:	oral 16%, intramuscular 73% and transdermal 88%

A highly selective, specific, and potent α_2 -adrenergic agonist (1,630:1 α_2 to α_1) that acts via a receptor distinct from the γ -aminobutyric receptor utilised by benzodiazepines and propofol. Offering dose-dependent sedation, anxiolysis, and analgesia. It can be used as a sedation in critical care, as an anaesthetic adjuvant, a procedural sedation, a premedication, and in the treatment of postoperative shivering and agitation.

It is a crucial regulator of vigilance and a major source of sympathetic nervous system innervation of the forebrain.

It has been explored more and used in a variety of clinical situations with encouraging outcomes due to its distinct pharmacological profile.

Dexmedetomidine, a selective α_2 -adrenergic receptor agonist, is a pharmacologically active dextroisomer of medetomidine that has a dose-dependent α_2 selectivity that is roughly 7-8 times higher than that of clonidine⁽³¹⁾, attaching to the brain and spinal cord's transmembrane G protein-binding adrenoreceptors (α_2B and α_2 adrenoreceptor). It also binds to imidazoline receptors, which may account for the actions of α_2 -adrenergic receptor agonists that are not related to α_2 adrenoreceptors⁽³⁰⁾.



[Figure 9: Physiology of Alpha-2 Adrenoceptors]

α_2 -Adrenergic receptor agonists have the properties of opioid sparing while also producing a variety of effects, including sedation and sympatholysis. In addition to mediating sedative and antinociceptive effects (α_{2A}) and a vasoconstrictive cardiovascular impact (α_{2B}), stimulation of the α_2 -adrenoceptor subtypes also modifies dopaminergic neurotransmission, hypothermia, and a range of behavioural responses (α_{2C})^(30,31).

As might be predicted for an α_2 -adrenergic receptor, the most frequent adverse effects of dexmedetomidine include bradycardia and hypotension. Sinus arrest and transient hypertension have been noticed during the induction of the loading dose of dexmedetomidine due to peripheral vasoconstrictive effects. Dexmedetomidine is cautiously administered in patients with ventricular dysfunction and advanced heart block or in coadministration with other vasodilators and negative chronotropic agents⁽³²⁾.

Mechanism of action:

Alpha-2 adrenoceptors are selectively and specifically agonistic to dexmedetomidine. It stops the transmission of pain signals by attaching itself to presynaptic alpha-1 adrenoceptors and blocking the release of norepinephrine. When postsynaptic alpha-2 adrenoceptors are activated, sympathetic activity is inhibited, lowering heart rate and blood pressure.

Pharmacokinetics:

It has a rapid distribution half-life of 6 minutes. The plasma protein binding of dexmedetomidine is about 94%.

Currently, dexmedetomidine is authorised for intravenous usage. However, other studies have investigated the value of using it in various ways. There are several well-established and increasingly common ways to give dexmedetomidine, including intrathecal, intranasal, oral, intramuscular, transdermal, and inhalational.

Metabolism :

Hepatic; largely metabolised by the liver by glucuronidation and oxidation via CYP2A6 and other cytochrome P450 enzymes. Used cautiously in patients with liver disease or hepatic impairment.

Distribution:

Distribution half-life is 6 minutes in adults with a volume of distribution of 1.3 L-2.46 L/kg.

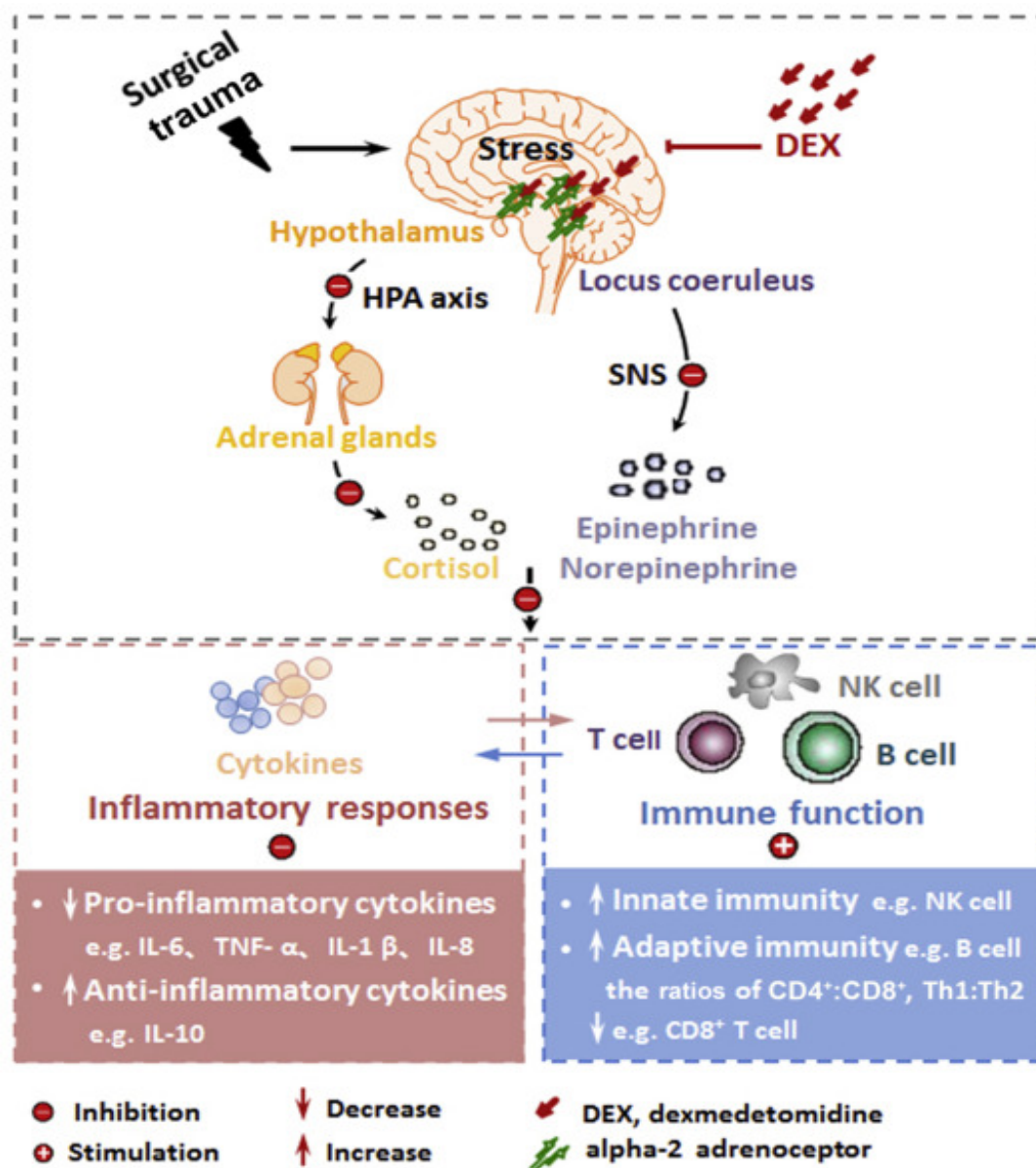
Elimination:

Excreted in the urine.

Dosaging

- For procedural sedation, 1 mcg/kg with maintenance dose of 0.6 mcg/kg/hr
- For sedation in the intensive care unit, 1 mcg/kg over 10 minutes, with a maintenance dosage of 0.2-0.7 mcg/kg/hr.

DEXMEDETOMIDINE on surgical stress



[Figure 10 : Dexmedetomidine of surgical stress]

A number of research studies have shown that dexmedetomidine reduces the central sympathetic outflow, thereby reducing the serum levels of norepinephrine and adrenaline, which reduces the stress reaction to intubation.

It suppresses the haemodynamic response to intubation and extubation without causing adverse effects like respiratory depression or postoperative nausea and

vomiting by activating receptors in the medullary vasomotor centre, lowering norepinephrine and regulating sympathetic outflow ^(10,44). Because dexmedetomidine reduced norepinephrine concentration, it caused a dose-dependent drop in heart rate and arterial blood pressure.

Studies have demonstrated that dexmedetomidine reduces surgical stress and inflammation, preserving the immunity of the patients. Dexmedetomidine infusion boosted the expression of NK cells, B cells, and CD4+ T cells but inhibited pro-inflammatory cytokine production, i.e., decreased the amounts of IL-6, TNF- α and CRP ⁽⁴⁴⁾ suggesting anti-inflammatory effects.

Anaesthesia augmented by dexmedetomidine reduced blood glucose, cortisol, norepinephrine and epinephrine levels, attenuating the postoperative stress response. Causing haemodynamic stability and decreased pancreatic insulin production via lowering cortisol and renin levels ⁽¹⁰⁾.

The anaesthetic and analgesic sparing effects of dexmedetomidine have been studied in both animals and humans. Dutta et al. reported a decrease in plasma concentration of 0.66 ng/ml of propofol needed for sedation and anaesthesia induction by 40 to 70% with the usage of dexmedetomidine. A single dose of 0.5 μ g/kg of dexmedetomidine has been shown to attenuate the rise in heart rate and MAP during laryngoscopy and tracheal intubation.

In conclusion, dexmedetomidine has shown promising results in controlling surgery and anaesthesia-associated stress, reducing inflammatory markers and improving immune function. Providing effective sedation and analgesia, reducing post-traumatic stress disorder in patients undergoing extensive surgery and alleviating anxiety. Dexmedetomidine is emerging as an apt drug for opioid-sparing techniques of anaesthesia.



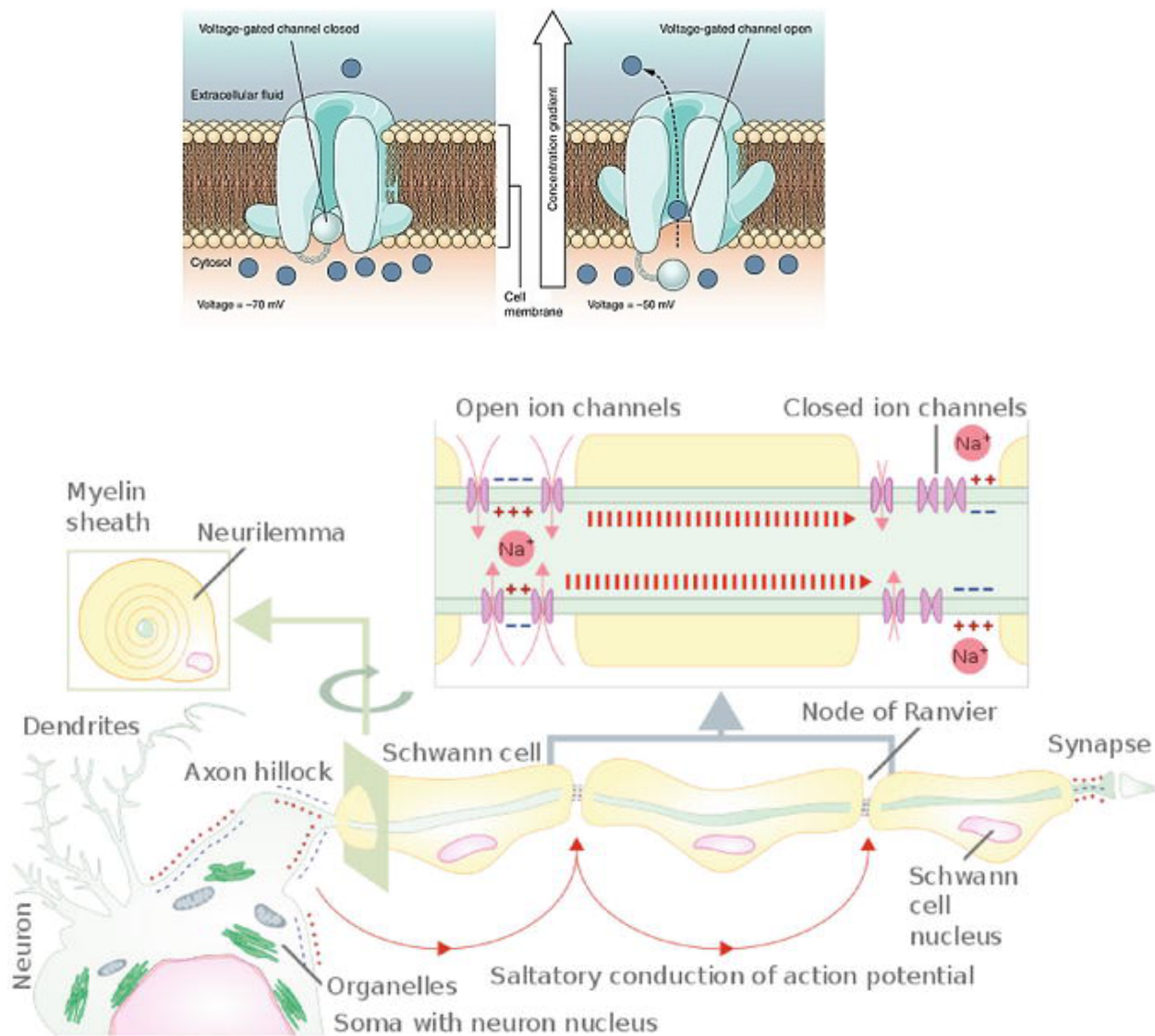
Generic name:	Lidocaine
Brand names:	Xylocaine, Loxicard
Bioavailability:	35% by mouth, 3% topical.
Metabolism:	Liver
Onset of action:	within 1.5 min (iv)
Duration of action:	10 to 20 mins (iv)
Excretion :	Kidneys

Lignocaine is a crystalline compound of $C_{14}H_{22}N_2O$ used in the form of its hydrochloride as a local anaesthetic and as an antiarrhythmic agent. It is a clear and colourless solution. A Swedish scientist created it for the first time in 1943 under the name Xylocaine, and it was first sold in 1949.

It is an amide-type local anaesthetic. It is employed in the ionic regulation of dysrhythmias and to produce local anaesthesia by blocking nerves at different parts of the body. It stabilises the neuronal membrane by preventing the ionic reflexes necessary for impulse initiation and conduction ⁽²⁷⁾.

Lignocaine has significant impacts on the central nervous system and cardiovascular system in addition to preventing conduction in peripheral nervous system nerve axons. Lignocaine operates mainly on the myocardium in the cardiovascular system, where it may result in reductions in electrical excitability, conduction rate, and contraction force. After absorption, it may cause stimulation of the central nervous system, followed by depression. It has a rapid onset and rapidly spreads through the surrounding tissues.

Mechanism of action: it blocks the ionic fluxes required for impulse initiation and conduction, hence providing nerve blockade at many body locations. It stabilises the neuronal membrane and produces a local anaesthetic effect. The sodium ion channels on the inside of nerve cell membranes are where the lignocaine chemical works. Through these channels, neutral, uncharged lignocaine molecules permeate the axoplasm through neural sheaths before becoming ionised by joining hydrogen ions. Because of this, if there is enough blockage, the postsynaptic neuron's membrane will eventually not depolarise and will not be able to convey an action potential ^(28,29).



[Figure 11: mechanism of action of Lignocaine]

Distribution:

The volume of distribution of lignocaine ranges from 0.7 to 1.5 L/kg. In comparison to other local anaesthetics, because it is 65% protein bound to albumin and α 1 acid glycoprotein in the plasma, lignocaine has a medium duration of action. It is distributed throughout the total body water. The drug's overall potency is limited because it is less lipid-soluble than other drugs. Higher concentrations of the agent will be seen in the organs that are more heavily perfused.

Metabolism:

Lignocaine is broken down into active and inactive molecules by the liver enzymes CYP1A2 and CYP3A4. The two main metabolites are glycylxylidide and monoethylglycylxylidide.

Elimination:

It is mostly eliminated by the kidney, where it is found in urine in its unaltered form. Its protein-binding affinity is inversely correlated with renal clearance

Dosaging:

- Infiltrative anaesthesia depends on specific block
- To obtund airway reflexes, 1 to 2 mg/kg
- For cardiac dysrhythmias, 1 to 1.5mg/kg followed by an infusion
- 1.5 mg/kg over 10 minutes for acute pain, then an infusion of no more than 1.5 mg/kg/hr for a maximum of 24 hours.

Lignocaine on surgical stress

Although the precise mechanism is unknown, lignocaine reduces inflammation, produces prolonged analgesic effects, reduces the need for opioids, and positively affects wound healing.

Leukocyte adhesion, migration, and activation can all be inhibited by lignocaine. By lowering the neutrophil adherence and preventing the generation of superoxide anions, it shields cells from inflammation.

Lignocaine reduces the expression of intercellular adhesion molecules and proinflammatory cytokines and may also have antineoplastic effects by inducing NK cells. According to studies, lignocaine lowers the levels of inflammatory indicators such as tumour necrosis factor- α , IL-1 and IL-6.

Perioperative intravenous lignocaine infusion lowers the requirement for opioids after surgery, effectively relieves pain, and attenuates the surgical stress response. It lowers the incidence of PONV

One important factor influencing perioperative mortality and morbidity is the stabilisation of intraoperative haemodynamic variables. Lignocaine has demonstrated efficacy in an anaesthetic regimen with a significant decrease in mean arterial pressure and cardiac index. It also inhibits catecholamine excretion without influencing cerebral blood flow ⁽⁴³⁾.

Studies have shown benefits of using lignocaine infusion in colorectal surgery as part of the ERAS protocol to promote gut motility and decrease opioid consumption ⁽⁴²⁾.

Physicians should take responsibility to cautiously administer the drug to reduce the risk of injury to patients, inculcate comorbidity screening, ensure close observation, provide appropriate dosaging, and have emergency drugs available.

Lignocaine may be a crucial complement to perioperative medicine as a non-opioid analgesic, with an affordable and easily accessible alternative to reduce the overuse of opioids in the treatment of multimodal analgesia and anaesthesia.

MATERIALS AND METHODS

SOURCE OF DATA

This study was carried out at Shri. B.M. Patil Medical College, hospital, and research centre in Vijayapura, in the Department of Anaesthesiology at BLDE (deemed to be university).

METHOD OF DATA COLLECTION

Study Method: A prospective comparative study.

A study population of 30 patients each group for a total sample size of 60 patients were selected to accomplish the sample size and placed into opioid-based general anaesthesia and opioid-free general anaesthesia groups.

Study period: Conducted from April 2023 to November 2024

Sample Size

[24] -- Friday, March 03, 2023 -- 15:22:21

t tests - Means: Difference between two independent means (two groups)

Analysis: A priori: Compute required sample size

Input: Tail(s) = Two

Effect size $d = 0.7605003$

α err prob = 0.05

Power ($1 - \beta$ err prob) = 0.82

Allocation ratio $N2/N1 = 1$

Output: Noncentrality parameter $\delta = 2.9454050$

Critical t = 2.0017175

Df = 58

Sample size group 1 = 30

Sample size group 2 = 30

Total sample size = 60

Actual power = 0.8254524

Sample size:

Using G*Power ver 3.1.9.4 software for sample size calculation, The HR of Intubation OB-

GA (Mean=90, SD=5 and OF-GA (Mean=85.8, SD=6).this study requires a total sample size of

60(for each group 30, assuming equal group sizes), so to achieve a power of 82% for detecting a

difference in Means t tests - Means: Difference between two independent means (two groups)

with 5% level of significance.

STATISTICAL ANALYSIS

- The data obtained is entered in a Microsoft Excel sheet, and statistical analyses are performed using a statistical package for the social sciences (SPSS) (Version 20).
- Results are presented as mean, SD, counts and percentages, and diagrams.
- For customarily distributed, continuous variables between the two groups were compared using an independent sample t-test.
- For not normally distributed variables, the Mann-Whitney U test is used.
- For categorical variables, the two groups are compared using the Chi-square test/Fisher's exact test.
- If $p < 0.05$ will be considered statistically significant. All statistics performed are two-tailed.

Blinding purposes—Based on the analgesia administered during the procedure, patients were divided into two study groups and assigned the following labels:

1-OB-GA: This group's patients were induced using 2 mg/kg of Inj Propofol and 0.5 mg/kg of Inj Atracurium. For intraoperative pain relief, 1-2 µg/kg of Inj Fentanyl was administered.

2-OF-GA: This group of patients received intraoperative DEX (1 µg/kg) and LID (20 mg/ml) infusion in addition to loading doses of dexmedetomidine (DEX 0.6 µg/kg) and lidocaine (LID 1.5 mg/kg) prior to intubation.

The clinical pathologist was blinded to the type of anaesthesia a patient who gave blood samples had received in order to ensure total blinding.

STUDY POPULATION: The study will be done in women of ASA grades I and II, requiring open abdominal hysterectomy.

INCLUSION CRITERIA:

- Women undergoing abdominal hysterectomy
- ASA grade I and II
- BMI <35 kg/m²

EXCLUSION CRITERIA:

- Difficult airway
- Contraindications to the drugs used.

METHODOLOGY:

Pre-Anaesthetic Evaluation:

- History: Information about underlying medical conditions, prior surgeries, anaesthetic exposure, and hospital stays was collected.
- Physical examination: General condition of the patient. Vital signs will be recorded: baseline heart rate, blood pressure, respiratory rate, mean arterial blood pressure, and body mass index.
- Examination of the upper and lower respiratory system, cardiovascular system, central nervous system, and vertebral system will be performed.
- Airway assessment by Mallampati grading done.
- Investigations included complete blood count, renal function test , random blood sugar and coagulation profile.

Pre-operatively:

- The patients were well-oxygenated with 100% oxygen at a 5 L/min flow rate for 3-5 minutes after receiving premedication: Inj Midazolam (0.03 mg/kg), Inj Glycopyrolate (0.008 mg/kg), and Inj Ondansetron (0.15 mg/kg).
- Venous blood sample were collected pre-operatively for estimation of serum interleukin C-Reactive protein (CRP), Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR)

Intraoperatively:

- Intraoperative respiratory rate, SpO₂ %, EtCO₂, heart rate, blood pressure and MAP were monitored.
- Time before induction was noted as T0 and vitals were monitored during induction and intubation at every 15-minute interval till extubation.

Post-operatively:

- Post-operatively, patients were shifted to PACU till complete recovery from anesthesia and vitals were monitored (respiratory rate, SpO₂%, Heart Rate, Blood pressure and MAP)
- Post-operative pain was evaluated utilising an 11-point numeric rating scale (NRS) starting at 0 and going up to 10, where 0 denotes no pain and 10 the worst possible pain. Every four hours for a 24-hour period, pain evaluations were performed from the time of discharge from the Post Anaesthesia Care Unit ⁽⁸⁾.
- The period of postoperative analgesia was established as the interval until the initial request for supplemental analgesia, administered in the form of a paracetamol infusion.
- Three-point vomiting and four-point nausea scores will be used to rate post-operative nausea and vomiting (PONV) ⁽⁹⁾. Patients who experienced severe nausea or vomiting received an intravenous infusion of ondansetron 4 mg.

Procedure:

Opioid Free - General Anaesthesia (OF-GA)⁽¹⁾: A loading dosage of 0.6 µg/kg of dexmedetomidine (DEX) was given, diluted to a volume of 10 cc in a syringe with a DEX label. In addition, a loading dose of 1.5 mg/kg of lidocaine (LID) was administered in a LID-labelled syringe that was diluted to a total amount of 10 cc for induction.

Continuous infusions were created for intraoperative management; the concentrations of the DEX and LID infusions were established at 1 µg/kg and 20 mg/ml, respectively. Depending on clinical needs, these infusions were given at rates between 0.2 to 0.7 µg/kg for DEX and 1-2 mg/kg/hr for LID, with modifications made as needed⁽⁷⁾.

Opioid-Based General Anaesthesia (OB-GA)⁽¹⁾: Anaesthesia was initiated with a dosage of propofol 2 mg/kg and a dosage of atracurium 0.5 mg/kg for patients undergoing obstetric general anaesthesia. For intraoperative pain management, fentanyl was administered at a dose of 1-2 µg/kg to the same patient group.

For individuals in both groups, tracheal intubation was facilitated through gentle pressure applied to the trachea, followed by the insertion of an endotracheal tube with a diameter ranging from 6.5 to 7.0 mm. After confirmation of endotracheal intubation by EtCO₂, anaesthesia was kept at 50% oxygen, 50% nitrous oxide and isoflurane 1% with intermittent doses of atracurium 0.1 mg/kg for both groups, with a semi-closed circle system. The muscle relaxant was antagonised by neostigmine at a dose of 0.05 mg/kg combined with Inj Glycopyrrolate at a dose of 0.008 mg/kg, leading to successful extubation with proper reversal.

INVESTIGATIONS AND INTERVENTIONS

Venous blood samples will be collected pre-operatively (S1) and at the 24-hour post-operative period (S2) under aseptic conditions in plain tubes and sent for C-reactive protein (CRP), Neutrophil Lymphocyte ratio (NLR) and Platelet Lymphocyte ratio (PLR).

OBSERVATIONS AND RESULTS

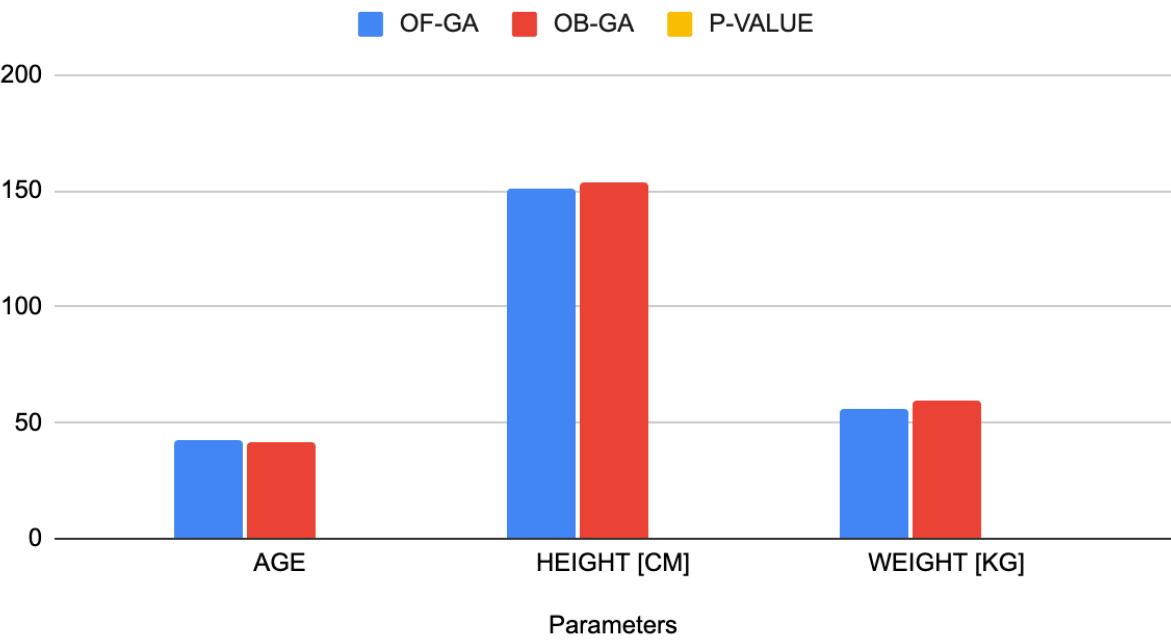
- The data collected from our study was represented in the master chart.
- A total sample size of 60 patients was collected. The OFA and OBA groups consisted of 30 patients each undergoing total abdominal hysterectomies.
- OFA: Patients of this group received general anaesthesia with a loading dose and infusion of Dexmedetomidine and Lignocaine.
- OBA: Patients of this group received general anaesthesia with a loading dose of Propofol and Fentanyl.
- A p-value below 0.05 was deemed statistically significant.

1. DEMOGRAPHIC VARIABLES:

	OFA		OBA		
Parameters	Mean	SD	Mean	SD	p-Value
Age [years]	42.87	7.78	41.97	7.815	0.657
Weight [Kg]	56.3	8.478	59.23	10.098	0.228
Height [Cm]	151.4	3.39	153.63	3.996	0.023

TABLE 4 : DEMOGRAPHIC DISTRIBUTION

OF-GA, OB-GA and P-VALUE



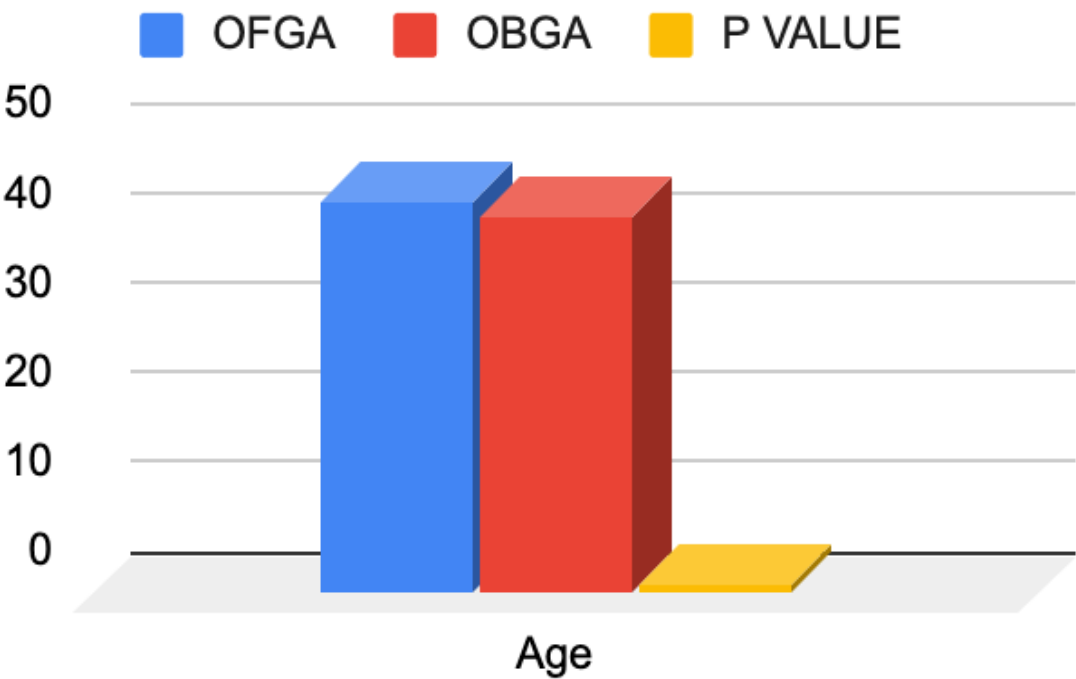
Graph 1: COMPARISON OF DEMOGRAPHIC VARIABLES: AGE, HEIGHT, AND WEIGHT

In terms of age and weight, the p-values were 0.657 and 0.228, respectively, which were statistically not significant. The p-value for height was 0.023 between OFA and OBA, which was statistically significant.

2. COMPARISON OF AGE DISTRIBUTION

	N	OF-GA	OB-GA	P-VALUE
AGE	30	42.87±7.780	41.97±7.815	0.657

TABLE 5: MEAN AGE OF TWO GROUPS



GRAPH 2: COMPARISON OF AGE DISTRIBUTION

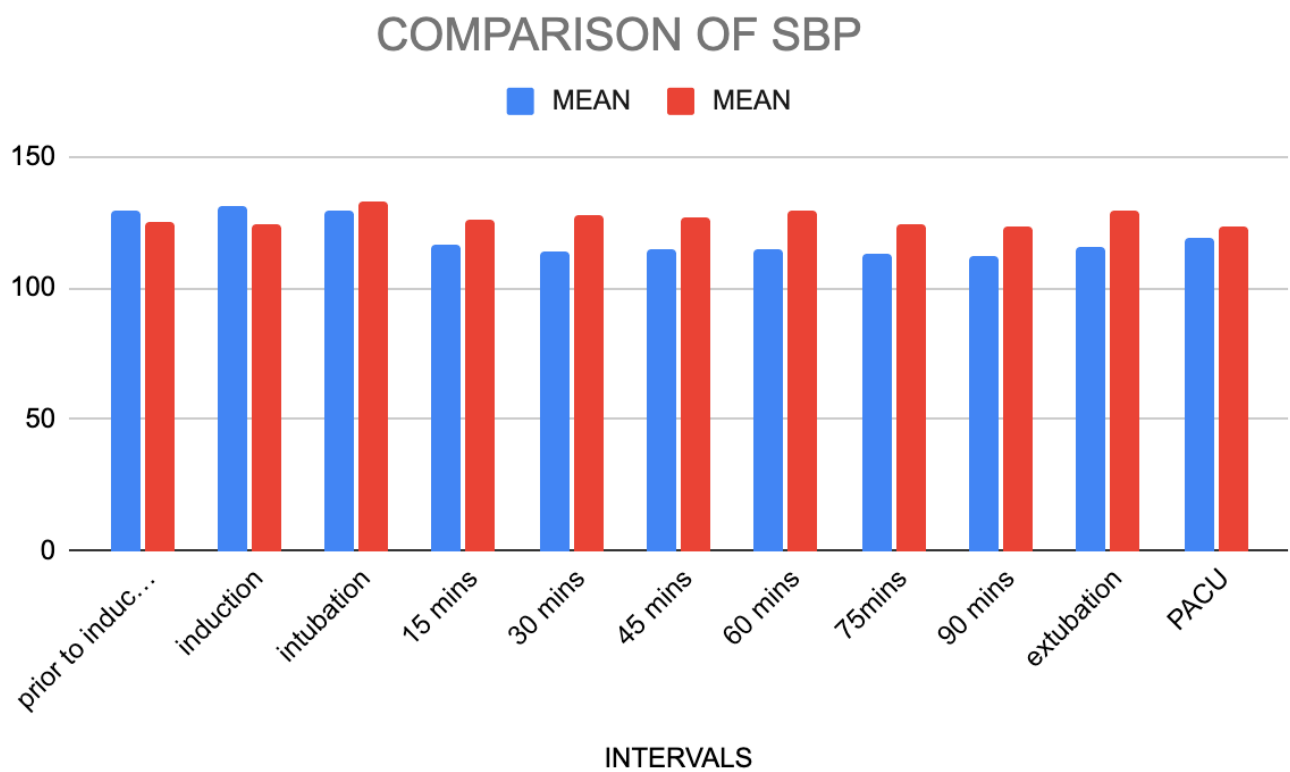
Age (years) of patients in the OFA and OBA groups were compared with a p-value of 0.657, indicating no statistical significance.

3. COMPARISON OF SYSTOLIC BLOOD PRESSURE IN OF and OB GROUPS AT VARYING INTERVALS INTRAOPERATIVELY

	SYSTOLIC BLOOD PRESSURE				
INTERVALS	OFA		OBA		P VALUE
	MEAN	SD	MEAN	SD	
Prior to induction	129.9	20.112	125.57	15.391	0.353
Induction	131.13	31.136	124	15.722	0.267
Intubation	129.3	22.301	132.73	15.768	0.494
15 mins	116.33	15.557	126.37	17.423	0.022
30 mins	114.27	13.997	127.33	17.684	0.002
45 mins	114.97	12.042	126.63	16.164	0.002
60 mins	115.07	13.102	129.43	14.119	0
75 mins	113.2	15.153	124.47	12.979	0.003
90 mins	112.33	13.902	123.47	13.833	0.003
Extubation	115.4	14.006	129.67	16.204	0.001
PACU	119.47	11.328	123.83	12.518	0.162

TABLE 6: DISTRIBUTION OF SBP BETWEEN OFA AND OBA GROUPS

The mean SBP among the OFA and OBA groups was statistically assessed using a T-test. The p-values obtained prior to induction, at induction and at intubation were statistically insignificant. Whereas from 15 minutes post-induction to extubation, p-values were found to be significant.



GRAPH 3: COMPARISON OF SBP AT VARYING INTERVALS INTRAOPERATIVELY IN BOTH OFA AND OBA GROUPS

The mean systolic blood pressures at different time intervals were plotted for each group. The mean SBP prior to induction, at induction and at intubation were almost similar for both the groups and deemed statistically insignificant. While the mean SBP was lower in the OFA (opioid-free) group at 15 mins, 30 mins, 45 mins, 60 mins, 75 mins and 90 mins time intervals and was statistically significant.

4. COMPARISON OF DIASTOLIC BLOOD PRESSURE IN OFA and OBA GROUPS AT VARYING INTERVALS INTRAOPERATIVELY

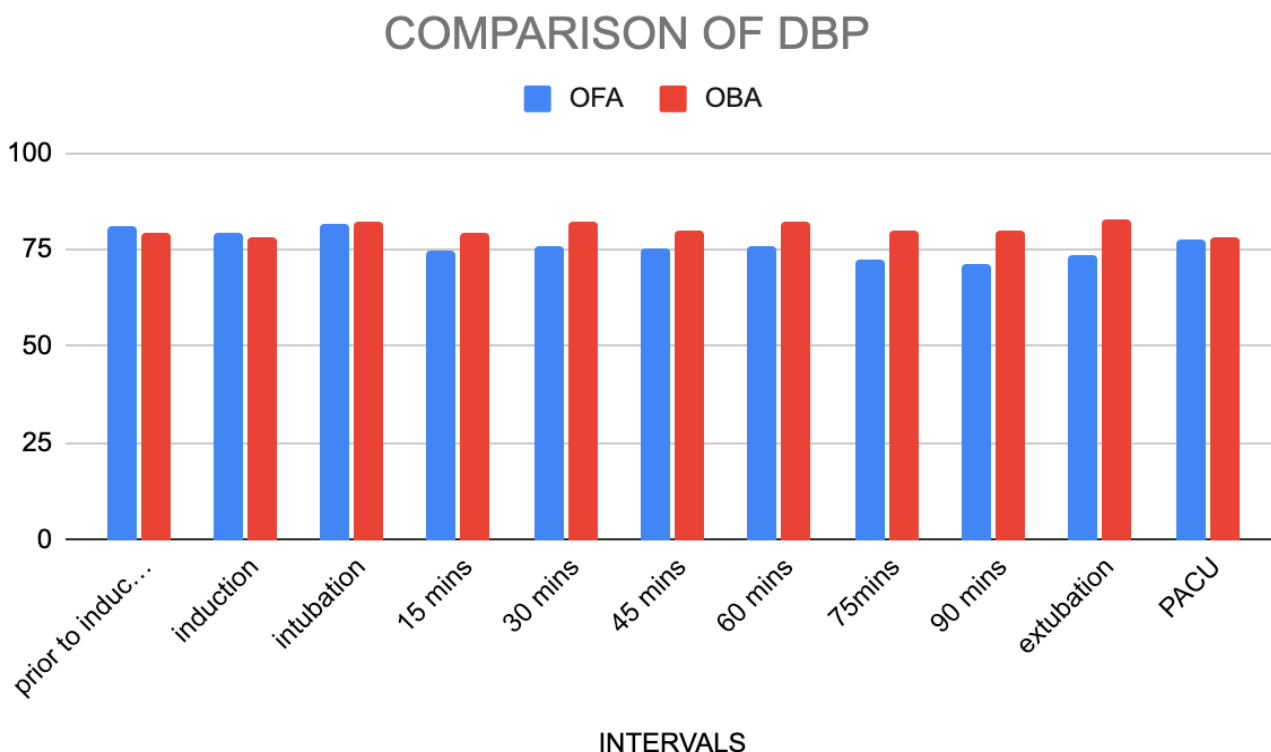
	DIASTOLIC BLOOD PRESSURE				
INTERVALS	OFA		OBA		P VALUE
	MEAN	SD	MEAN	SD	
Prior to induction	81.4	9.737	79.53	8.905	0.442
Induction	79.6	17.395	77.97	7.989	0.642
Intubation	81.67	15.257	82.47	8.216	0.801
15 mins	74.7	12.922	79.3	8.441	0.108
30 mins	75.7	9.535	82.23	10.348	0.014
45 mins	75.2	9.715	80.23	10.424	0.058
60 mins	76	10.882	82.2	8.814	0.018
75mins	72.63	12.705	80.2	9.144	0.01
90 mins	71.47	10.712	79.87	7.399	0.001
Extubation	73.9	11.376	82.83	10.313	0.002
PACU	77.4	8.966	78.33	8.648	0.683

TABLE 7: DISTRIBUTION OF DBP FOR OFA AND OBA GROUPS

The mean diastolic blood pressure was assessed using a T-test.

Statistically insignificant p-values were obtained for both groups prior to induction, at induction, at intubation and at 15-minute intervals.

Whereas significant p-values were obtained at 30 minutes, 45 minutes, 60 minutes, 75 minutes, 90 minutes, and at extubation.



GRAPH 4: COMPARISON OF DBP AT VARYING INTERVALS INTRAOPERATIVELY IN BOTH OFA AND OBA GROUPS

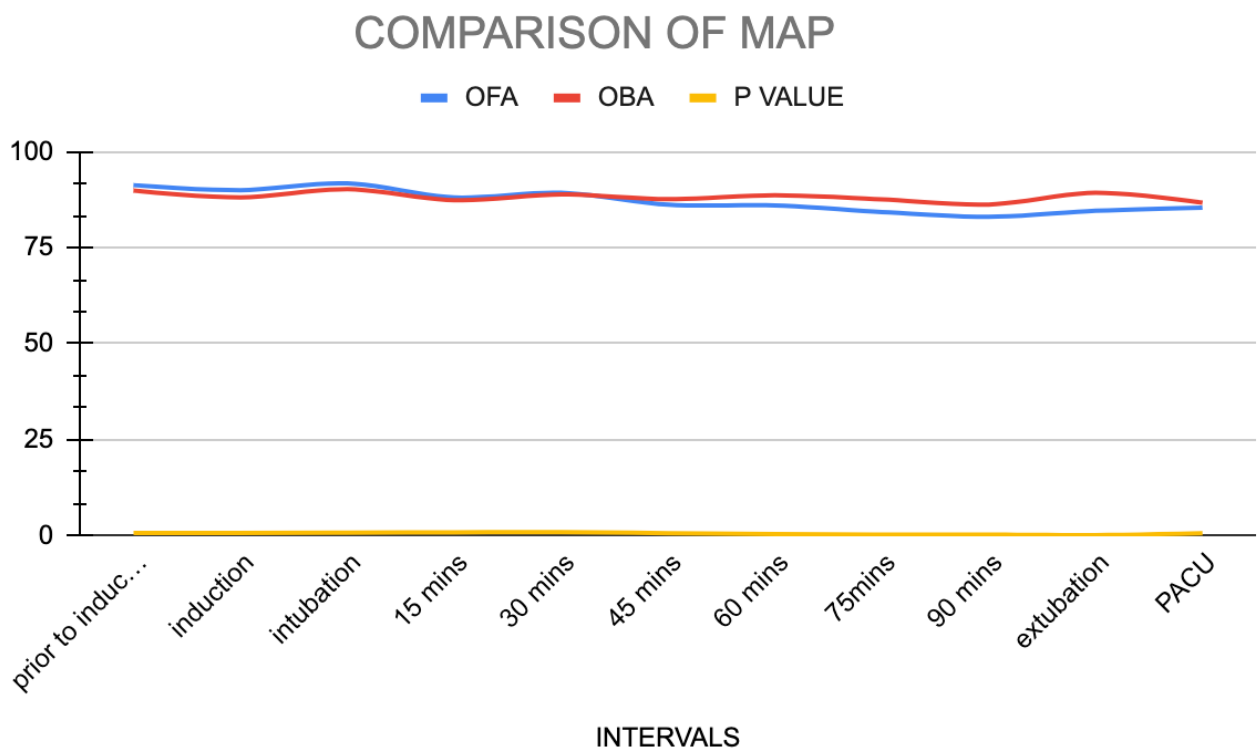
The mean diastolic blood pressures at different time intervals were plotted for each group. The mean DBP prior to induction, at induction, at intubation and at 15 minutes were similar and statistically insignificant. While the mean DBP at 30 minutes, 45 minutes, 60 minutes, 75 minutes, 90 mins and at extubation was lower in the OFA (opioid-free) group and statistically significant.

5. COMPARISON OF MEAN ARTERIAL PRESSURE AT VARYING INTERVALS AFTER GENERAL ANAESTHESIA

	MEAN ARTERIAL PRESSURE				
INTERVALS	OFA		OBA		P VALUE
	MEAN	SD	MEAN	SD	
Proior to induction	91.33	14.221	89.93	13.421	0.696
Induction	90.03	20.552	88.13	11.802	0.662
Intubation	91.8	11.332	90.27	11.332	0.727
15 mins	88.13	14.936	87.4	9.651	0.822
30 mins	89.33	14.325	88.9	12.598	0.901
45 mins	86.23	10.846	87.67	12.181	0.632
60 mins	86.03	10.88	88.67	11.009	0.355
75 mins	84.33	11.484	87.63	10.257	0.245
90 mins	83.07	10.491	86.27	10.082	0.233
Extubation	84.63	10.669	89.33	11.333	0.104
PACU	85.43	10.779	86.77	8.423	0.595

TABLE 8: DISTRIBUTION OF MEAN ARTERIAL PRESSURE IN OFA AND OBA GROUP

The mean MAP was plotted for the OFA and OBA groups and deemed statistically insignificant as the p-values were more than 0.05, respectively.



GRAPH 5: COMPARISON OF MAP OFA OF AND OBA GROUP AT VARYING INTERVALS INTRAOPERATIVELY

The mean MAP among OFA and OBA groups assessed by T-test was statistically insignificant. The p-values obtained were more than 0.005.

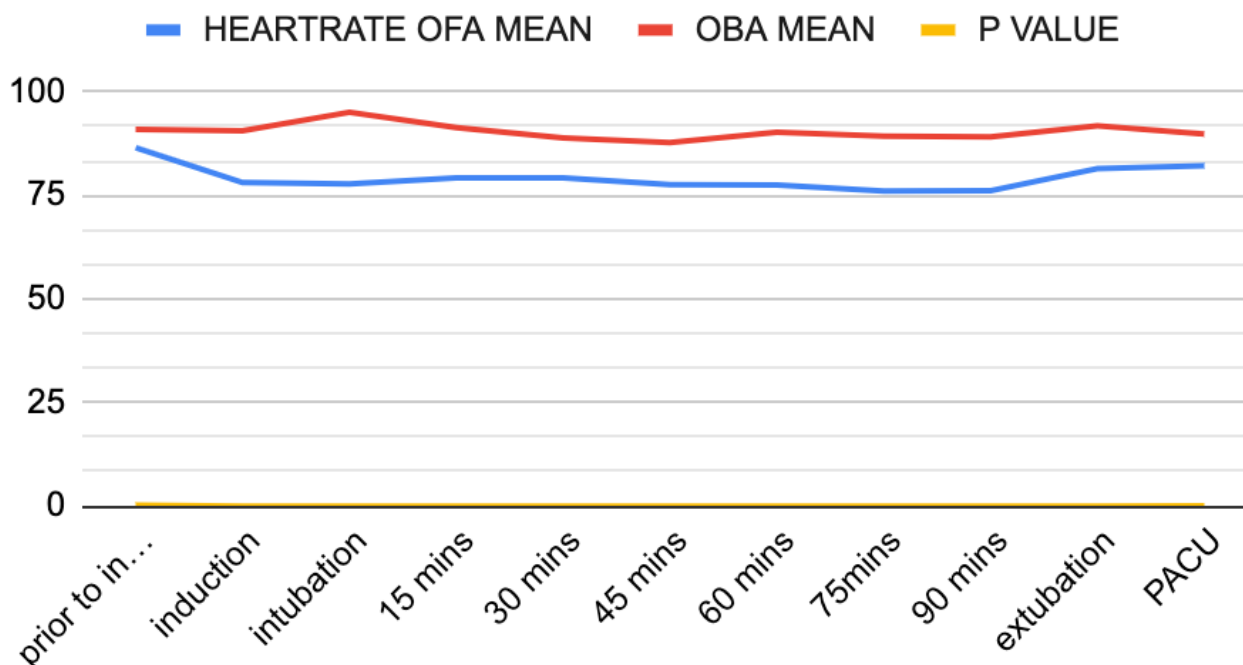
6. COMPARISON OF HEART RATE BETWEEN OF and OB GROUPS

	HEARTRATE				
INTERVALS	OFA		OBA		P VALUE
	MEAN	SD	MEAN	SD	
Prior to induction	86.5	14.867	90.93	15.916	0.269
Induction	78.1	16.748	90.57	14.853	0.003
Intubation	77.77	14.426	95.03	13.75	0
15 mins	79.23	13.263	91.4	12.147	0
30 mins	79.2	11.645	88.9	14.552	0.006
45 mins	77.57	10.494	87.77	15.787	0.005
60 mins	77.47	9.677	90.21	13.644	0
75mins	76.03	9.29	89.3	12.46	0
90 mins	76.1	9.799	89.17	14.65	0
Extubation	81.5	11.776	91.8	12.815	0.002
PACU	82.17	13.956	89.8	12.77	0.031

TABLE 9: DISTRIBUTION OF HEART RATE IN OFA AND OBA GROUPS

The average heart rates for each group were evaluated through a T-test. A significant p-value below 0.05 was achieved at different time points. An insignificant p-value was obtained prior to induction of 0.269.

COMPARISON OF HEART RATES



GRAPH 6: COMPARISON OF HEART RATES OF OFA AND OBA GROUPS AT VARYING INTERVALS INTRAOPERATIVELY

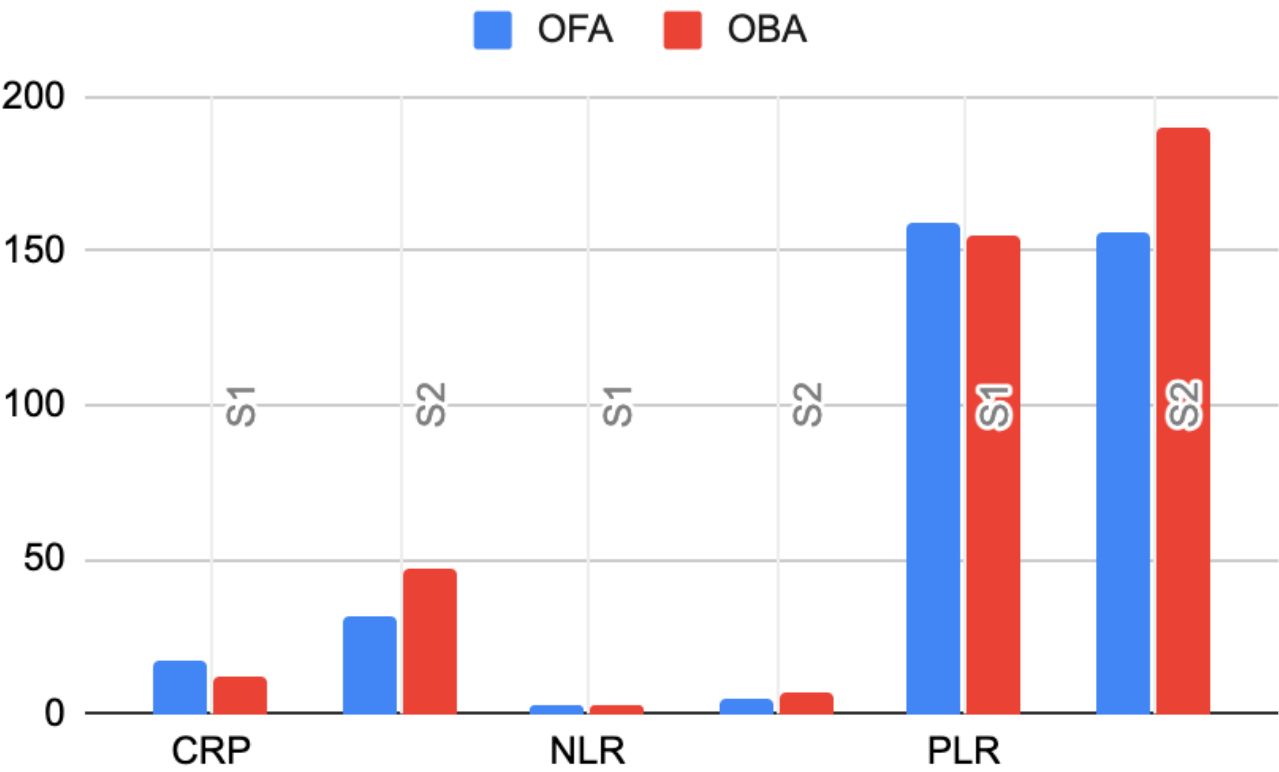
The mean heart rates at varying time intervals intraoperatively were plotted for each group. The mean heart for the OBA (opioid-based) group was higher when compared to OFA (opioid-free) group. The obtained p-values were statistically significant from induction till post-operative period.

7. COMPARISON OF INFLAMMATORY MARKERS PREOPERATIVELY AND POSTOPERATIVELY AFTER GENERAL ANESTHESIA IN OFA VS OBA

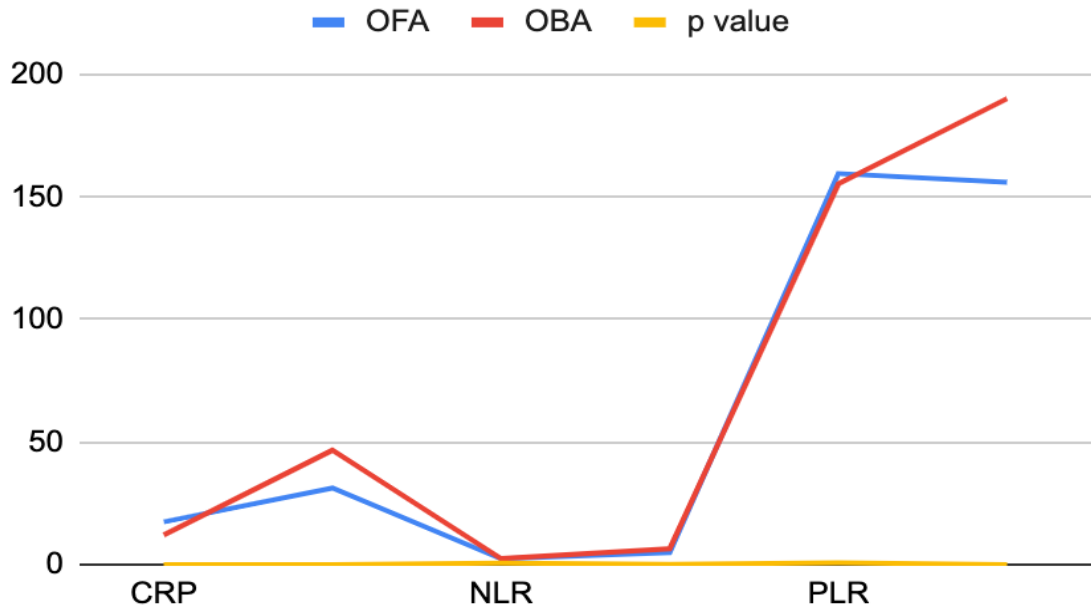
		INFLAMMATORY MARKERS				
		OFA		OBA		
		MEAN	SD	MEAN	SD	p-value
CRP	S1	17.5	14.0078	12.1625	7.425	0.0703
	S2	31.282	18.1658	46.75	13.852	0.0005
NLR	S1	2.4333	1.1943	2.533	0.8995	0.7162
	S2	4.9333	2.4625	6.5	4.9323	0.1250
PLR	S1	159.548	84.9679	155.383	54.8807	0.8224
	S2	155.984	75.1272	190.20553	82.90083	0.0992

TABLE 10: COMPARISON OF INFLAMMATORY MARKERS

The mean values for inflammatory markers were collected for both groups before and after the surgery, showing a significant difference between the preoperative and postoperative values, while the p-values for CRP in preoperative phase was insignificant, the postoperative value was statistically significant. Additionally, the mean values of NLR and PLR demonstrated significance in the postoperative period for both groups, although their p-values were statistically insignificant.



GRAPH 7 AND 8 COMPARISON OF INFLAMMATORY MARKERS PREOPERATIVELY AND POSTOPERATIVELY FOR OFA AND OBA GROUPS



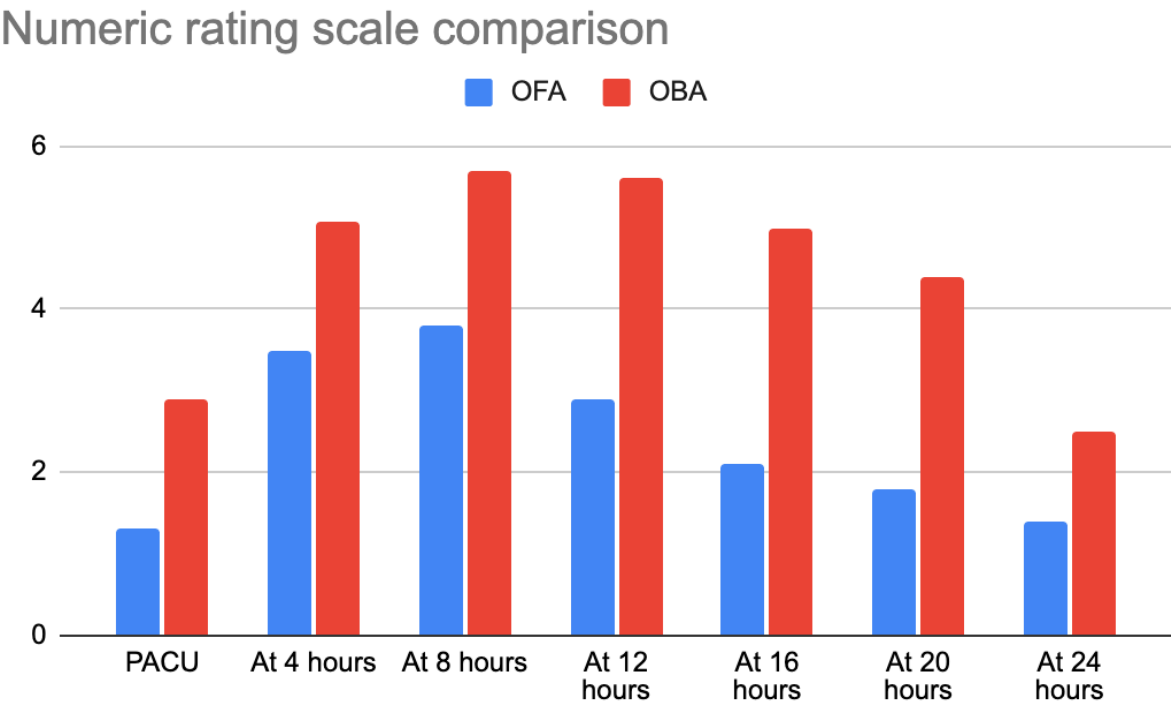
8. COMPARISION OF POSTOPERATIVE PAIN SCORES USING NRS

	OFA (N=30)		OBA (N=30)		
Intervals	mean	SD	mean	SD	p-value
PACU	1.3	1.1	2.9	0.8	$P < 0.0001$
At 4 hours	3.5	0.8	5.06	0.7	$P < 0.0001$
At 8 hours	3.8	0.9	5.7	0.5	$P < 0.0001$
At 12 hours	2.9	0.9	5.6	0.8	$P < 0.0001$
At 16 hours	2.1	0.5	5	0.7	$P < 0.0001$
At 20 hours	1.8	0.6	4.4	0.8	$P < 0.0001$
At 24 hours	1.4	0.5	2.5	0.9	$P < 0.0001$

Table 11: Comparison of NRS between OFA & OBA

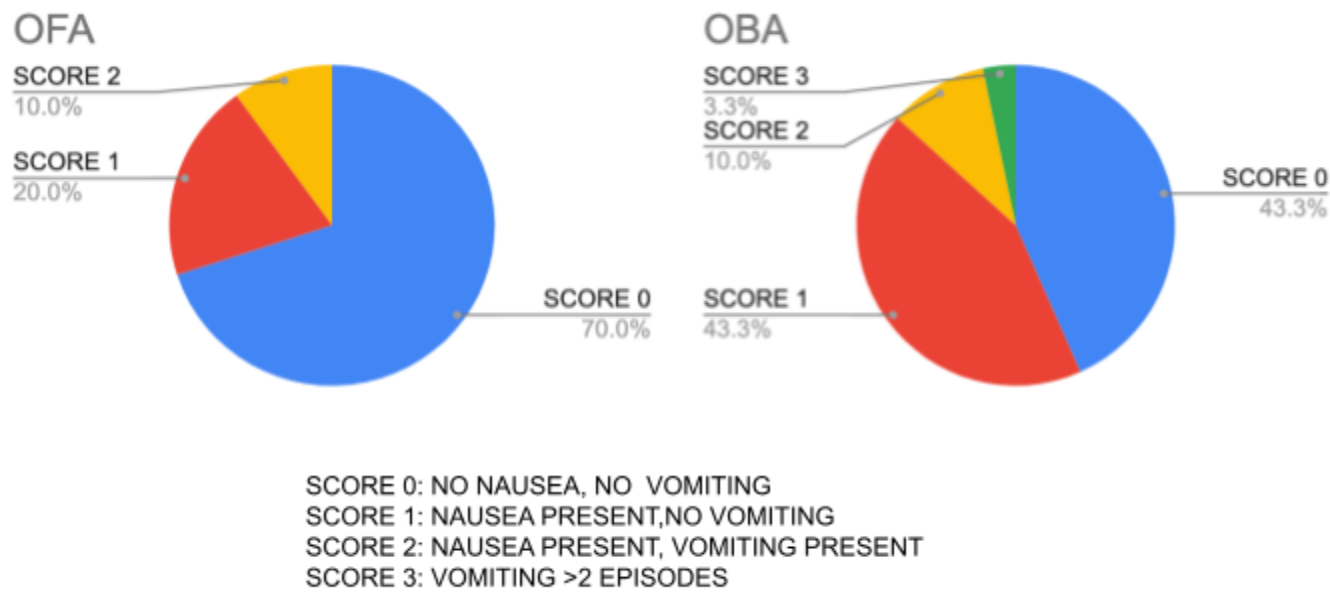
In the context of a Numeric Rating Scale (NRS), where lower values typically correspond to more favourable outcomes, such as reduced pain or discomfort, the data reveal that the OFA group consistently reported lower scores across all measured intervals in comparison to the OBA group.

The statistical analysis reveals that these differences are not only present but also statistically significant, with extremely low p-values ($P < 0.0001$) obtained for all measured intervals. The statistical significance of these differences ($p < 0.0001$) emphasizes the reliability of the findings between the two groups.



Graph 9: NRS complex at different interval periods
The NRS scale showing OF group showing a steady rise in pain over a longer duration , in comparison to the immediate requirement of rescue analgesia in OB group

9. COMPARISON OF POSTOPERATIVE NAUSEA AND VOMITING



GRAPH 10: COMPARISON OF POST-OPERATIVE NAUSEA AND VOMITING SEVERITY SCORES.

In the conducted study, postoperative nausea and vomiting scores were significantly lower in the group that did not receive opioids compared to the opioid-administered group. Specifically, fourteen patients in the opioid-based group experienced nausea, and six reported vomiting. In the opioid-free group, eight patients experienced nausea, while three reported vomiting

DISCUSSION

The existing body of literature indicates that various anaesthetic agents and techniques employed during surgical procedures can influence the host's innate and adaptive immune systems ⁽²⁾. The specific anaesthetic method significantly affects the activity of postoperative immune cells, including macrophages, neutrophils, dendritic cells, natural killer cells and T-cells.

Compared to opioid-based intraoperative analgesia, dexmedetomidine-based analgesia provided better perioperative control over the inflammatory response caused by surgery, longer postoperative analgesia and decreased need for rescue analgesia.

The purpose of this study was to demonstrate an opioid-free anaesthesia method using dexmedetomidine and lignocaine, to demonstrate fewer perioperative issues. Including mild changes in intraoperative haemodynamics, decreased postoperative complications, pain and opioid consumption in patients undergoing abdominal procedures under general anaesthesia.

This study noticed that the use of opioids resulted in a notable increase in postoperative inflammatory markers when compared to the preoperative levels. There is sufficient evidence from various studies that supports the decrease in inflammatory markers in postoperative period with the usage of opioid-free anaesthesia. Yang et al. found that when used perioperatively, dexmedetomidine reduces inflammatory markers (IL-6 and TNF- α) ⁽⁴⁸⁾.

Results showed that there was minimal variation in haemodynamic parameters compared to the opioid-based group. At varying intervals from induction to extubation, it was noted that there was no significant variation in haemodynamic parameters, although, in the opioid-free group, it was noticed that there was no drastic or steep variation in systolic blood pressure or heart rate.

According to Neil L, Ashok patl, et al.⁽⁴⁴⁾ dexmedetomidine is a better drug compared to the usage of opioids for maintaining haemodynamic responses during intubation and in the intraoperative period.

While a degree of hypotension and bradycardia was observed during the bolus infusion of dexmedetomidine, attributed to the suppression of the sympathetic nervous system, these effects were promptly rectified through the tapering of the dexmedetomidine infusion and the immediate intravenous administration of 0.6 mg of Inj atropine. I.e; it is dose dependant.

Intraoperatively, observation was made that the MAC value for inhalational agents experienced a significant decrease in the opioid-free group. A MAC range of 0.6 to 0.4 for isoflurane was sustained.

At 24 hours following surgery, the pain levels measured using the Numeric Rating scale (NRS) in the opioid-free group were found to be considerably lower than those in the opioid-based group. Additionally, the requirement for rescue analgesia occurred significantly later in the opioid-free group. Mujukian et al ⁽⁴⁷⁾. Stated, multimodal analgesia that includes opioid-sparing medications is a successful strategy for lowering pain and perioperative opioid use following invasive colorectal surgery

In contrast, the opioid-based group exhibited a greater number of requests for analgesia during the postoperative period as compared to the opioid-free group. According to Bello et al ⁽⁴⁶⁾. Opioid-free anaesthesia lowers the need for opioids during thoracotomy, early postoperative pain scores and anaesthetic consumption.

Dexmedetomidine offers several advantages in the treatment of postoperative nausea and vomiting (PONV). Its antiemetic effect may be attributed to the direct properties of α_2 agonists, which inhibit catecholamine release through the modulation of parasympathetic tone. Some studies suggest that lignocaine may have a beneficial effect on reducing PONV, however the exact mechanism is elusive.

With this, a notable decrease in the occurrence of postoperative nausea and vomiting (PONV) with the usage of dexmedetomidine and lignocaine was seen in our study. According to our conducted study, 14 patients in the opioid-based group experienced nausea, and 6 patients reported vomiting. In contrast, the opioid-free group has 8 patients with nausea and 3 patients with vomiting. These episodes were treated with an intravenous administration of Inj Ondansetron 4mg.

Numerous studies have demonstrated that Dexmedetomidine serves as an effective analgesic and a reliable anxiolytic agent. Additionally, research indicates that the use of dexmedetomidine is associated with reduced perioperative stress, diminished inflammatory responses, lower incidence of postoperative nausea and vomiting (PONV), and a decrease in cognitive dysfunctions.

CONCLUSION

Intraoperative dexmedetomidine-based analgesia resulted in longer postoperative analgesia with a lesser requirement of rescue analgesia, decreased episodes of nausea and vomiting, and better control over the inflammatory markers induced by surgery.

Enhancement of sensory function in patients from anaesthesia, minimisation of opioid usage, preservation of haemodynamic stability throughout the perioperative period, alleviation of postoperative pain and facilitation of prompt recovery were some of the advantages of opioid-free anaesthesia over opioid-based anaesthesia.

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ETHICAL CLEARANCE



BLDE

(DEEMED TO BE UNIVERSITY)

Declared as Deemed to be University u/s 3 of UGC Act, 1956

Accredited with 'A' Grade by NAAC (Cycle-2)

The Constituent College

SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

BLDE (DU)/IEC/ 953/2023-24

10/4/2023

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this University met on **Saturday, 18th March, 2023 at 11.30 a.m.** in the **CAL Laboratory, Dept. of Pharmacology**, scrutinized the Synopsis/ Research Projects of Post Graduate Student / Under Graduate Student / Faculty members of this University / Ph.D. Student College from ethical clearance point of view. After scrutiny, the following original/ corrected and revised version synopsis of the thesis/ research projects has been accorded ethical clearance.

TITLE: "EVALUATION OF OPIOID FREE ANAESTHESIA IN CUTAILING POSTOPERATIVE SERUM LEVELS OF INFLAMMATORY MARKERS AND PROVIDING POST-OPERATIVE ANALGESIA IN OPEN ABDOMINAL HYSTERECTOMIES-A PROSPECTIVE COMPARATIVE STUDY".

NAME OF THE STUDENT/PRINCIPAL INVESTIGATOR: DR.SANDRA THOMAS

NAME OF THE GUIDE: DR.VIDYA PATIL, PROFESSOR AND HOD, DEPT. OF ANAESTHESIOLOGY.

Dr. Santoshkumar Jeevangi
Chairperson
IEC, BLDE (DU),
VIJAYAPURA

Chairman,
Institutional Ethical Committee,
BLDE (Deemed to be University)
Vijayapura

Dr. Akram A. Naikwadi
Member Secretary
IEC, BLDE (DU),
VIJAYAPURA

MEMBER SECRETARY
Institutional Ethics Committee
BLDE (Deemed to be University)
Vijayapura-586103, Karnataka

Following documents were placed before Ethical Committee for Scrutinization.

- Copy of Synopsis/Research Projects
- Copy of inform consent form
- Any other relevant document

Smt. Bangaramma Sajjan Campus, B. M. Patil Road (Sholapur Road), Vijayapura - 586103, Karnataka, India.

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ANNEXURE - I

SAMPLE OF INFORMED CONSENT FORM:

**BLDE (DEEMED TO BE UNIVERSITY), SHRI B.M.PATIL MEDICAL COLLEGE
HOSPITAL AND RESEARCH CENTER, VIJAYAPURA-586103, KARNATAKA**

**TITLE OF PROJECT: EVALUATION OF OPIOID-FREE ANAESTHESIA
IN CURTAILING POSTOPERATIVE SERUM LEVELS OF
INFLAMMATORY MARKERS AND PROVIDING POSTOPERATIVE
ANALGESIA IN OPEN ABDOMINAL HYSTERECTOMIES -A
PROSPECTIVE COMPARATIVE STUDY**

**PRINCIPAL INVESTIGATOR: DR SANDRA THOMAS
JUNIOR RESIDENT
Department of Anesthesiology
BLDE(DU), Shri B.M Patil Medical College Hospital
Vijayapura, Karnataka**

**PG GUIDE: DR VIDYA PATIL
MD -Anesthesiology
PROFESSOR- Department of Anesthesiology
BLDE(DU), Shri B.M Patil Medical College Hospital
Vijayapura, Karnataka**

PURPOSE OF RESEARCH:

I have been informed that in this study the comparison of Dexmedetomidine-based intraoperative analgesia provided a better perioperative control on reducing the inflammatory markers response, prolonged post-operative analgesia and reduced need for rescue analgesia.

I have been explained about the need for doing this study and the reason for selecting me/my ward as a subject for this study. I have also been given the free choice of either being included or not in the study.

PROCEDURE:

I understand that I will be taking part in the study: EVALUATION OF OPIOID FREE ANAESTHESIA IN CURTAILING POSTOPERATIVE SERUM LEVELS OF INFLAMMATORY MARKERS AND PROVIDING POSTOPERATIVE ANALGESIA IN OPEN ABDOMINAL HYSTERECTOMIES -A PROSPECTIVE COMPARATIVE STUDY

RISKS AND DISCOMFORTS:

I understand that I/my ward participating in the study may experience some discomfort during the procedure, and I know that necessary measures will be taken to reduce them.

BENEFITS:

I understand that me/my ward participating in this study will help in finding out the EVALUATION OF OPIOID FREE ANAESTHESIA IN CURTAILING POSTOPERATIVE SERUM LEVELS OF INFLAMMATORY MARKERS AND PROVIDING POSTOPERATIVE ANALGESIA IN OPEN ABDOMINAL HYSTERECTOMIES -A PROSPECTIVE COMPARATIVE STUDY.

CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of this hospital's records and will be subjected to the confidentiality and privacy regulations of this hospital. If the data is used for publication in the medical literature or for teaching purposes, no names will be used and other identifiers such as photographs and audio or video tapes will be used only with my special written permission. I understand that I may see the photograph and videotapes and hear audio tapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time to Dr. Sandra Thomas as she is available to answer my questions and concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation. If during this study or later I wish to discuss my participation in or concerns regarding the study with someone not directly involved, I am aware that the social worker of the hospital is available to talk with me and that a copy of this consent form will be given to me for a careful reading.

REFUSAL OR WITHDRAWAL OR PARTICIPATION:

I understand that my participation is voluntary, and I may refuse to participate or withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital.

I also understand that Dr. Sandra Thomas can terminate my participation in this study at any time after he has explained the reason for doing so and has helped arrange for my continued care by my physician or therapist if this is appropriate.

INJURY STATEMENT:

I understand that in the unlikely event of injury to me/ my ward, resulting directly due to my participation in this study, the such injury will be reported promptly and the medical treatment will be available to me/my ward, but no further compensation will be provided.

I understand that by my agreement to participate in this study, I am not waiving my legal rights. I have been explained about the purpose of this research, the procedure required and the possible risk and benefits to the best of my abilities and my language of understanding.

Date:

Dr Sandra Thomas
(Investigator)

Patient/Parent signature

Witness

STUDY SUBJECT CONSENT STATEMENT:

I confirm that Dr. SANDRA THOMAS has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience in the language of my understanding.

I have been explained all the above in detail in my language of understanding and I understand the same. Therefore I agree to give consent to participate as a subject in this research project.

(Participant)

(Date)

B.L.D.E (DEEMED TO BE UNIVERSITY) ಶ್ರೀ ಬಿ.ಎಂ.ಪಟ್ಟೇಲ್

ಮೆಡಿಕಲ್ ಕಾಲೇಜು, ಆಸ್ಪತ್ರೆ ಮತ್ತು ಸಂಶೋಧನಾ ಕೇಂದ್ರ, ವಿಜಯಪುರ-586103

ಪ್ರಬಂಧ/ಸಂಶೋಧನೆಯಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ಮಾಹಿತಿ ಪಡೆದ ಸಮ್ಮತಿ

ನಾನು, ಕೆಳಗಿನವರು _____ ಸಹಿಯಿಟ್ಟವರು, ಮಗ/ಮಗಳು/ಪತ್ನಿಯು _____ ವಯಸ್ಸು _____ ವರ್ಷಗಳು, ಸಾಮಾನ್ಯವಾಗಿ ನಿವಾಸಿಸುವ ಸ್ಥಳದ ಹೆಸರು _____, ಇಲ್ಲಿ ಹೇಳಿದ್ದೇನೆ/ಘೋಷಿಸುತ್ತೇನೆ ಡಾಕ್ಟರ್ ಹೆಸರು _____ ಅವರು ಆಸ್ಪತ್ರೆ ಹೆಸರು _____ ಅವರು ನನ್ನನ್ನು ಪೂರ್ಣವಾಗಿ ಪರೀಕ್ಷಿಸಿದರು ದಿನಾಂಕದಲ್ಲಿ _____ ಸ್ಥಳ ಹೆಸರು _____ ಮತ್ತು ನನಗೆ ನನ್ನ

ಭಾಷೆಯಲ್ಲಿ ವಿವರಿಸಲಾಗಿದೆ ನಾನು ಒಂದು ರೋಗ (ಸ್ಥಿತಿ) ಅನುಭವಿಸುತ್ತಿದ್ದೇನೆ. ಮುಂದುವರಿದು ಡಾಕ್ಟರ್ ನನಗೆ ತಿಳಿಸಿದ್ದಾರೆ ಅವರು ಒಂದು ಪದ್ಧತಿ/ಸಂಶೋಧನೆ ನಡೆಸುತ್ತಿದ್ದಾರೆ ಶೀರ್ಷಿಕೆಯುಳ್ಳ _____ ಡಾಕ್ಟರ್ _____ ಮಾರ್ಗದರ್ಶನದಲ್ಲಿ ನನ್ನ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆಯನ್ನು ಕೇಳಿದ್ದಾರೆ ಅಧ್ಯಯನದಲ್ಲಿ.

ಡಾಕ್ಟರ್ ನನಗೆ ಇದನ್ನು ಕೂಡಾ ತಿಳಿಸಿದ್ದಾರೆ ಈ ಕ್ರಮದ ನಡೆವಳಿಕೆ ಪ್ರತಿಕೂಲ ಫಲಿತಾಂಶಗಳನ್ನು ಎದುರಿಸಬಹುದು. ಮೇಲೆ ಹೇಳಿದ ಪ್ರಕಟಣೆಗಳಲ್ಲಿ, ಅಧಿಕಾಂಶವು ಚಿಕಿತ್ಸಿಸಬಹುದಾದರೂ ಅದನ್ನು ನಿರೀಕ್ಷಿಸಲಾಗುತ್ತಿಲ್ಲ ಆದ್ದರಿಂದ ನನ್ನ ಸ್ಥಿತಿಯ ಹಿರಿದಾಗುವ ಅವಕಾಶವಿದೆ ಮತ್ತು ಅಪರೂಪದ ಸಂದರ್ಭಗಳಲ್ಲಿ ಅದು ಮರಣಕಾರಕವಾಗಿ ಪರಿಣಮಿಸಬಹುದು ಹೊಂದಿದ ರೋಗ ನಿರ್ಧಾರ ಮತ್ತು ಯಥಾಶಕ್ತಿ ಚಿಕಿತ್ಸೆ ಮಾಡಲು ಹೊಂದಿದರೂ. ಮುಂದುವರಿದು ಡಾಕ್ಟರ್ ನನಗೆ ತಿಳಿಸಿದ್ದಾರೆ ನನ್ನ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆ ಈ ಅಧ್ಯಯನದ ಫಲಿತಾಂಶಗಳ

ಮೌಲ್ಯಮಾಪನದಲ್ಲಿ ಸಹಾಯಕವಾಗುತ್ತದೆ ಇತರ ಸಮಾನ ಪ್ರಕರಣಗಳ ಚಿಕಿತ್ಸೆಗೆ ಉಪಯುಕ್ತ ಉಲ್ಲೇಖವಾಗಿದೆ, ಮತ್ತು ನಾನು ಅನುಭವಿಸುವ ರೋಗದಿಂದ ವಿಮುಕ್ತಿ ಅಥವಾ ಗುಣಮುಖಗೊಳ್ಳುವಲ್ಲಿ ನನಗೆ ಪ್ರಯೋಜನವಾಗಬಹುದು.

ಡಾಕ್ಟರ್ ನನಗೆ ಇದನ್ನು ಕೂಡಾ ತಿಳಿಸಿದ್ದಾರೆ ನನ್ನಿಂದ ನೀಡಿದ ಮಾಹಿತಿ, ಮಾಡಿದ ಪರಿಶೀಲನೆಗಳು / ಫೋಟೋಗ್ರಾಫ್ಗಳು / ವೀಡಿಯೋ ಗ್ರಾಫ್ಗಳು ನನ್ನ ಮೇಲೆ ತೆಗೆದುಕೊಳ್ಳಲಾಗುವ ಅನ್ವೇಷಕರು ರಹಸ್ಯವಾಗಿ ಇಡುವರು ಮತ್ತು ನಾನು ಅಥವಾ ನನಗೆ ಕಾನೂನು ದೃಷ್ಟಿಯಲ್ಲಿ ಸಂಬಂಧಿತರನ್ನು ಹೊರತುಪಡಿಸಿ ಇತರ ವ್ಯಕ್ತಿಯಿಂದ ಮೌಲ್ಯಮಾಪನ ಮಾಡಲಾಗುವುದಿಲ್ಲ. ಡಾಕ್ಟರ್ ನನಗೆ ತಿಳಿಸಿದ್ದಾರೆ ನನ್ನ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆ ಶುದ್ಧವಾಗಿ ಸ್ವೇಚ್ಛಾಯಿತ, ನನ್ನಿಂದ ನೀಡಿದ ಮಾಹಿತಿಯ ಆಧಾರದ ಮೇಲೆ, ಚಿಕಿತ್ಸೆ / ಅಧ್ಯಯನದ ಸಂಬಂಧದಲ್ಲಿ ರೋಗ ನಿರ್ಧಾರ, ಚಿಕಿತ್ಸೆಯ ವಿಧಾನ, ಚಿಕಿತ್ಸೆಯ ಫಲಿತಾಂಶ ಅಥವಾ ಆ ಭವಿಷ್ಯದ ಪ್ರವೃತ್ತಿಗಳು ಬಗ್ಗೆಯಾವುದೇ ಸ್ಪಷ್ಟತೆ ಕೇಳಬಹುದು. ಅದೇ ಸಮಯದಲ್ಲಿ ನನಗೆ ತಿಳಿಸಲಾಗಿದೆ ನಾನು ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಈ

ಅಧ್ಯಯನದಲ್ಲಿ ನನ್ನ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆಯನ್ನು ನಿಲ್ಲಿಸಬಹುದು ನಾನು ಬಯಸಿದರೆ ಅಥವಾ ಅನ್ವೇಷಕರು ಅಧ್ಯಯನದಿಂದ ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ನನ್ನನ್ನು ನಿಲ್ಲಿಸಬಹುದು.

ಪ್ರಬಂಧ ಅಥವಾ ಸಂಶೋಧನೆಯ ಸ್ವಭಾವ, ಮಾಡಿದ ರೋಗ ನಿರ್ಧಾರ ಮತ್ತು ಚಿಕಿತ್ಸೆಯ ವಿಧಾನವನ್ನು ಅರ್ಥಮಾಡಿಕೊಂಡು, ನಾನು ಕೆಳಗಿನ ಶ್ರೀ / ಶ್ರೀಮತಿ _____ ನನ್ನ ಪೂರ್ಣವಾದ ಪ್ರಜ್ಞೆಯ ಸ್ಥಿತಿಯಲ್ಲಿ ಹೇಳಿದ ಸಂಶೋಧನೆ / ಪ್ರಬಂಧದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ಒಪ್ಪುತ್ತೇನೆ.

ರೋಗಿಯ ಸಹಿ ಡಾಕ್ಟರನ ಸಹಿ

ಸಾಕ್ಷಿಗಳು

1)

2)

ANNEXURE - II

SCHEME OF CASE TAKING

STUDY: EVALUATION OF OPIOID-FREE ANAESTHESIA IN CURTAILING POSTOPERATIVE SERUM LEVELS OF INFLAMMATORY MARKERS AND PROVIDING POST-OPERATIVE ANALGESIA IN OPEN ABDOMINAL HYSTERECTOMIES -A PROSPECTIVE COMPARATIVE STUDY.

PROFORMA:

PATIENT DETAILS:

NAME	
AGE	
SEX	
WEIGHT	
HEIGHT	
WARD	
DIAGNOSIS	
PROCEDURE	
PAST HISTORY	

GENERAL EXAMINATION:

PALLOR	ICTERUS	CYANOSIS	CLUBBING	EDEMA	LYMPHADENOPATHY

VITALS:

PULSE	BLOOD PRESSURE	RESPIRATORY RATE	TEMPERATURE
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--	--	--	--

SYSTEMIC EXAMINATION

CVS	
RS	
CNS	
PA	

AIRWAY ASSESSMENT:

MALLAMPATI SCORE:	CERVICAL SPINE:
MOUTH OPENING:	NECK MOVEMENTS:

INVESTIGATIONS:

BMI:	
ASA	
HB	PLT
S UREA	S CREATININE
RBS	
CXR	ECG

PARAMETERS

Time	HR	BP	SPO2	ETCO2
Prior to induction T0				
Induction				
Intubation				
15 mins				
30 mins				
45 mins				
60 mins				
75 mins				
90 mins				
Extubation				
PACU				

INFLAMMATORY MARKERS

	S1	S2
CRP		
NLR		
PLR		

(S1- pre-operative sample, S2- 24 hours post-operative)

IL-6: Interleukin-6; CRP- C-Reactive protein, NLR- Neutrophil Lymphocyte ratio, PLR- Platelet Lymphocyte ratio.

Pain assessment:**Using NRS pain scale:**

	PAIN SCALE (NRS)
0-4 hours	
4-8 hours	
8-12 hours	
12-16 hours	
16-20 hours	
20-24 hours	

Postoperative Nausea - Vomiting

Score	Nausea and vomiting degree
0	No nausea, no vomiting
1	Nausea present, no vomiting
2	Nausea present, vomiting present
3	Vomiting >2 episodes in 30 min

	PRESENT	ABSENT	SEVERITY
NAUSEA			
VOMITING			

BIODATA

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MASTER CHART

Sl No:	NAME	IP number	DEMOGRAPHIC VARIABLES			DIAGNOSIS	PROCEDURE	COMORBS	Parameters	HEART RATE	
			Age	Weight [KG]	HEIGHT					prior to induction	induction
1	NEELAMMA	11074	45	65	155CM	I	A3 with multiple fibroids	NIL	1	80	83
2	KAVITA	12019	26	60	145CM	I		NIL	2	86	90
3	SANGAMMA	17356	46	55	148CM	I	AUB-L	NIL	3	110	68
4	SUVARNA	190763	40	60	152CM	I	AUB	NIL	4	83	90
5	SAVITA	22390	43	56	150CM	I	Fibroid uterus with mod anaemia	NIL	5	80	55
6	ROMARABI	65505	46	65	154CM	II	AUB-A with hbSag+ with mod anaemia	hbSag+	6	110	68
7	MAHDA	32654	46	55	155CM	I	Right serous cystadenoma	ANAEMIA	7	80	68
8	MUMTAZ		44	55	157CM	I	Acute PID	NIL	8	72	74
9	GOURAMMA	364991	43	50	150CM	I	AUB	NIL	9	80	82
10	LAXMIBAI		65	50	146CM	II	Right Simple ovarian cyst	HTN	10	80	86
11	SUNITA	335004	39	70	145CM	I	Serous Cyst Adenoma	NIL	11	96	63
12	RENUKA	169569	42	55	154CM	I	AUB-A	NIL	12	88	88
13	REVAMMA	173750	45	40	150CM	II	Mass per abdomen	HIV	13	84	60
14	LALITHABAI	173773	45	65	155CM	I	Uterine Fibroid with adenomyosis	NIL	14	68	53
15	SABAVVA	184480	37	50	158CM	I	PID	NIL	15	97	93
16	DEVAMMA	231477	38	60	154CM	II	AUB-L	hypothroidism	16	92	92
17	RENUKA	87215	54	70	154cm	I	AUB-E	NIL	17	73	74
18	KALAVATHI	85519	62	50	148CM	I	Chronic PID	NIL	18	72	68
19	MALLAMMA	205151	47	54	152CM	I	AUB-E	NIL	19	68	53
20	AVANAMMA		34	80	152CM	II	Ruptured Ovarian mass	RHDV/ALVULAR	20	110	106
21	NIRMALA	97124	100686	42	55	152CM	II	Chronic PID	21	86	66
22	GOURAVVA		39	60	148CM	II	AUB-E	NIL	22	80	86
23	KASHIBAI	151009	41	46	150CM	II	LEIOMYOMA	NIL	23	68	53
24	NAZAMIN	262122	33	50	150CM	I	AUB-L	MR	24	86	90
25	SUJANDA	167391	50	54	148CM	I	AUB-E	SEVERE ANAEMIA	25	125	120
26	SUDHARANI	26587	40	55	150CM	I	AUB-E	NIL	26	112	90
27	NIRMALA	306792	37	40	146cm	I	ADENOMYOSIS	NIL	27	73	74
28	KAMALABAI	185537	40	55	152CM	II	Left Ovarian Cyst	NIL	28	78	80
29	KASTURI	337773	41	54	154CM	I	Acute on chronic PID	TZDM	29	84	60
30	SUREKHA	120570	36	65	148CM	I	CHRONIC PID	NIL	30	100	102

[illegible]

60 mins		75mins		90 mins		exubation PACU		Parameters ETCO2		prior to induction		induction		intubation		15mins		30 mins		45 mins		60 mins		75mins		90 mins		exubation PACU		SL NO		S/L6		S2 IL6								
100%	100%	100%	100%	100%	100%	100%	98%	1	-	-	-	-	-	36	36	35	37	39	36	36	36	36	36	36	36	36	36	36	33	-	1	-	-	-								
100%	100%	100%	100%	100%	100%	100%	98%	2	-	-	-	-	-	36	35	34	36	37	38	36	36	36	36	36	36	36	36	35	-	2	-	-	-	-								
100%	100%	100%	100%	100%	100%	100%	98%	3	-	-	-	-	-	36	34	35	38	32	34	34	34	34	34	34	34	34	32	-	3	-	-	-	-	-								
100%	100%	100%	100%	100%	100%	100%	98%	4	-	-	-	-	-	36	34	36	36	36	36	36	36	36	36	36	36	36	34	-	4	-	-	-	-	-	-							
100%	100%	100%	100%	100%	100%	100%	98%	5	-	-	-	-	-	32	34	32	28	28	27	28	27	28	28	28	28	27	28	-	5	-	-	-	-	-	-							
100%	100%	100%	100%	100%	100%	100%	98%	6	-	-	-	-	-	32	30	30	29	31	30	29	30	29	30	29	30	30	30	-	6	-	-	-	-	-	-							
100%	100%	100%	100%	100%	100%	100%	97%	7	-	-	-	-	-	36	34	34	34	36	36	36	36	36	36	36	36	34	-	7	-	-	-	-	-	-	-							
100%	100%	100%	100%	100%	100%	100%	98%	8	-	-	-	-	-	36	36	33	34	35	33	31	33	31	33	31	33	31	33	-	8	-	-	-	-	-	-	-						
100%	100%	100%	100%	100%	100%	100%	99%	9	-	-	-	-	-	34	32	34	32	30	30	30	32	30	30	32	32	32	-	9	-	-	-	-	-	-	-	-						
100%	100%	100%	100%	100%	100%	100%	100%	10	-	-	-	-	-	32	30	30	29	31	30	29	30	29	30	29	30	30	30	-	10	-	-	-	-	-	-	-	-					
100%	100%	100%	100%	100%	100%	100%	98%	11	-	-	-	-	-	58	55	56	48	48	45	42	42	42	42	45	42	42	-	11	-	-	-	-	-	-	-	-	-					
100%	100%	100%	100%	100%	100%	100%	100%	12	-	-	-	-	-	32	32	32	30	30	30	32	32	30	30	30	32	32	-	12	-	-	-	-	-	-	-	-	-					
100%	100%	100%	100%	100%	100%	100%	100%	13	-	-	-	-	-	34	32	32	30	32	34	34	34	34	34	34	34	32	-	13	-	-	-	-	-	-	-	-	-					
100%	100%	100%	100%	100%	100%	100%	97%	14	-	-	-	-	-	32	34	32	30	30	30	34	34	34	34	34	34	32	-	14	-	-	-	-	-	-	-	-	-					
100%	100%	100%	100%	100%	100%	100%	100%	15	-	-	-	-	-	36	34	34	34	32	34	34	34	34	34	34	34	34	34	-	15	-	-	-	-	-	-	-	-	-				
100%	100%	100%	100%	100%	100%	100%	100%	16	-	-	-	-	-	38	35	34	32	32	32	32	32	32	32	32	32	32	32	-	16	-	-	-	-	-	-	-	-	-				
100%	100%	100%	100%	100%	100%	100%	100%	17	-	-	-	-	-	34	32	30	32	32	30	30	30	30	30	30	30	34	-	17	-	-	-	-	-	-	-	-	-	-				
100%	100%	100%	100%	100%	100%	100%	100%	18	-	-	-	-	-	34	32	30	32	32	30	32	30	30	30	30	30	34	-	18	-	-	-	-	-	-	-	-	-	-	-			
100%	100%	100%	100%	100%	100%	100%	100%	19	-	-	-	-	-	32	34	32	30	30	30	34	34	34	34	34	34	32	-	19	-	-	-	-	-	-	-	-	-	-	-			
98%	98%	98%	98%	98%	98%	98%	96%	20	-	-	-	-	-	30	30	28	28	28	34	34	34	34	34	32	32	-	20	-	-	-	-	-	-	-	-	-	-	-	-	-		
100%	100%	100%	100%	100%	100%	100%	100%	21	-	-	-	-	-	32	30	30	29	31	30	29	30	29	30	29	30	30	-	21	-	-	-	-	-	-	-	-	-	-	-	-		
100%	100%	100%	100%	100%	100%	100%	100%	22	-	-	-	-	-	34	32	30	32	32	30	30	32	32	30	30	34	-	22	-	-	-	-	-	-	-	-	-	-	-	-	-		
100%	100%	100%	100%	100%	100%	100%	100%	23	-	-	-	-	-	36	35	34	36	37	38	36	36	36	36	35	35	-	23	-	-	-	-	-	-	-	-	-	-	-	-	-		
100%	100%	100%	100%	100%	100%	100%	100%	24	-	-	-	-	-	28	30	29	29	29	29	29	28	28	28	28	28	-	24	-	-	-	-	-	-	-	-	-	-	-	-	-		
100%	100%	100%	100%	100%	100%	100%	100%	25	-	-	-	-	-	28	27	28	26	25	25	25	25	25	25	25	26	-	25	-	-	-	-	-	-	-	-	-	-	-	-	-		
100%	100%	100%	100%	100%	100%	100%	100%	26	-	-	-	-	-	34	32	30	32	30	32	30	30	30	32	30	30	34	-	26	-	-	-	-	-	-	-	-	-	-	-	-	-	
100%	100%	100%	100%	100%	100%	100%	100%	27	-	-	-	-	-	34	32	30	32	30	32	30	30	30	32	30	30	34	-	27	-	-	-	-	-	-	-	-	-	-	-	-	-	
100%	100%	100%	100%	100%	100%	100%	100%	28	-	-	-	-	-	34	32	32	30	32	34	34	34	34	34	34	32	-	28	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
100%	100%	100%	100%	100%	100%	100%	100%	29	-	-	-	-	-	36	35	34	36	37	38	36	36	36	35	35	35	-	29	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
100%	100%	100%	100%	100%	100%	100%	100%	30	-	-	-	-	-	32	32	30	32	34	34	32	34	34	34	34	32	-	30	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

N/E	at 16 hours	at 20 hours	at 24 hours	SL NO	PONV		Severity
					NAUSEA	Vomiting	
	3	3	3		1 ABSENT	ABSENT	SCORE 0
	2	2	1		2 PRESENT	ABSENT	SCORE 1
	3	3	2		3 ABSENT	ABSENT	SCORE 0
	4	3	2		4 ABSENT	ABSENT	SCORE 0
	4	2	2		5 ABSENT	ABSENT	SCORE 0
	3	2	1		6 PRESENT	ABSENT	SCORE 1
	2	1	1		7 ABSENT	ABSENT	SCORE 0
	2	1	1		8 ABSENT	ABSENT	SCORE 0
	3	1	1		9 ABSENT	ABSENT	SCORE 0
	3	2	1		10 PRESENT	PRESENT	SCORE 2
	4	3	2		11 ABSENT	ABSENT	SCORE 1
	2	2	1		12 PRESENT	ABSENT	SCORE 0
	3	2	1		13 PRESENT	PRESENT	SCORE 2
	4	3	3		14 ABSENT	ABSENT	SCORE 0
	3	2	1		15 ABSENT	ABSENT	SCORE 0
	4	3	1		16 ABSENT	ABSENT	SCORE 0
	4	4	3		17 ABSENT	ABSENT	SCORE 0
	2	2	1		18 ABSENT	ABSENT	SCORE 0
	3	1	1		19 ABSENT	ABSENT	SCORE 0
	3	2	2		20 PRESENT	ABSENT	SCORE 1
	2	1	1		21 ABSENT	ABSENT	SCORE 0
	2	2	1		22 ABSENT	ABSENT	SCORE 0
	2	1	1		23 ABSENT	ABSENT	SCORE 0
	2	1	1		24 ABSENT	ABSENT	SCORE 0
	2	2	1		25 ABSENT	ABSENT	SCORE 0
	4	3	3		26 PRESENT	ABSENT	SCORE 1
	2	2	1		27 ABSENT	ABSENT	SCORE 1
	3	2	1		28 PRESENT	PRESENT	SCORE 2
	2	2	1		29 ABSENT	ABSENT	SCORE 0
	2	2	1		30 ABSENT	ABSENT	SCORE 0

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