ASSOCIATION BETWEEN OPIUM USE DISORDER AND POSTOPERATIVE COMPLICATIONS IN PATIENTS UNDERGOING SURGERY IN GENERAL SURGERY DEPARTMENT OF A TERTIARY CARE CENTRE:

A PROSPECTIVE COHORT STUDY



# THESIS Submitted to

All India Institute of Medical Sciences, Jodhpur
In partial fulfillment of the requirement for the degree of
MASTER OF SURGERY (MS)
GENERAL SURGERY

JULY, 2020 AIIMS, JODHPUR

DR. M.V.R. ABHISHEK

# ASSOCIATION BETWEEN OPIUM USE DISORDER AND POSTOPERATIVE COMPLICATIONS IN PATIENTS UNDERGOING SURGERY IN GENERAL SURGERY DEPARTMENT OF A TERTIARY CARE CENTRE: A PROSPECTIVE COHORT STUDY



## Thesis Submitted to

All India Institute of Medical Sciences, Jodhpur
In partial fulfilment of the requirement for the degree of
Master of Surgery (MS)
General Surgery

July 2020 AIIMS, Jodhpur

Dr. M.V.R. ABHISHEK

# ASSOCIATION BETWEEN OPIUM USE DISORDER AND POSTOPERATIVE COMPLICATIONS IN PATIENTS UNDERGOING SURGERY IN GENERAL SURGERY DEPARTMENT OF A TERTIARY CARE CENTRE: A PROSPECTIVE COHORT STUDY



#### **Thesis**

#### Submitted to

All India Institute of Medical Sciences, Jodhpur
In partial fulfilment of the requirement for the degree of
Master of Surgery (MS)

**General Surgery** 

Dr. M.V.R. Abhishek

Junior Resident

**Department of General Surgery** 

AIIMS, Jodhpur

Dr. Mahendra Lodha

**Additional Professor** 

**Department of General Surgery** 

AIIMS, Jodhpur

**July 2020** 

All India Institute of Medical Sciences, Jodhpur



#### **DECLARATION**

I hereby declare that this thesis titled "Association between opium use disorder and postoperative complications in patients undergoing surgery in general surgery department of a tertiary care center: a prospective cohort study" is a bonafide and original research work carried out in partial fulfilment of the requirements for the degree of Masters of Surgery in General Surgery under supervision and guidance, in the Department of General Surgery, All India Institute of Medical Sciences, Jodhpur.

Dr. M.V.R. Abhishek

Department of General Surgery

All India Institute of Medical Sciences, Jodhpur



### **CERTIFICATE**

This is to certify that the thesis titled "Association between opium use disorder and postoperative complications in patients undergoing surgery in general surgery department of a tertiary care center: a prospective cohort study" is the bonafide work of Dr. M.V.R. Abhishek carried out under our guidance and supervision, in the Department of General Surgery, All India Institute of Medical Sciences, Jodhpur.

Additional Professor

Department of General Surgery

AIIMS, Jodhpur



## **CERTIFICATE**

This is to certify that the thesis titled "Association between opium use disorder and postoperative complications in patients undergoing surgery in general surgery department of a tertiary care center: a prospective cohort study" is the bonafide work of Dr. M.V.R. Abhishek carried out under our guidance and supervision, in the Department of General Surgery, All India Institute of Medical Sciences, Jodhpur.

Guide M. W. W. W. W.

Additional Professor

Department of General Surgery

AIIMS, Jodhpur



#### **CERTIFICATE**

This is to certify that the thesis titled "Association between opium use disorder and postoperative complications in patients undergoing surgery in general surgery department of a tertiary care centre: a prospective cohort study" is the bonafide work of Dr. M.V.R. Abhishek carried out under our guidance and supervision, in the Department of General Surgery, All India Institute of Medical Sciences, Jodhpur.

Co Guide

Dr. Navratan Suthar

**Associate Professor** 

Department of Psychiatry



#### **DECLARATION**

This is to certify that this thesis titled "Association between opium use disorder and postoperative complications in patients undergoing surgery in general surgery department of a tertiary care centre: a prospective cohort study" is a bonafide and original research work carried out by Dr. M.V.R. Abhishek under supervision and guidance, in the Department of General Surgery. All India Institute of Medical Sciences, Jodhpur.

Dr. Naveen Sharma

Professor and Head

Department of General Surgery AIIMS, Jodhpur

### <u>ACKNOWLEDGEMENT</u>

I had no idea that I would be a part of this distinguished institute when I began my post graduate entrance preparation. It is only because of the unending drive of my mentors, family, and co-workers that I have been able to follow my quest for surgical knowledge while also completing my thesis work with pride and satisfaction.

This is not a solo effort. The credit must go to everyone, both named and unnamed, who has been with me from the beginning to the end of this project.

I'd want to begin by thanking **God** for gifting me with the education, wisdom, vision, capability, knowledge, and desire to attain my objectives.

My greatest thanks go out to **Dr. Mahendra Lodha**, Additional Professor of the Department of General Surgery at the All India Institute of Medical Sciences in Jodhpur, who served as my mentor and adviser during the preparation of this dissertation for my postgraduate study. With his straightforward yet inventive teaching style, advice on academic research, unique surgical procedures, and kind demeanour, he has never failed to inspire all of us.

For his unwavering encouragement and support throughout the study, my co-guide **Dr.**Navratan Suthar, Associate Professor, Department of Psychiatry, All India Institute of Medical Sciences, Jodhpur, has my deepest gratitude.

For his assistance with statistical analysis and kindness always, **Dr. Akhil Dhanesh Goel**, Additional Professor, Department of Community Medicine, All India Institute of Medical Sciences, Jodhpur, is also acknowledged.

I want to express my gratitude to the entire Department of General Surgery at AIIMS Jodhpur for making me feel at home.

I would like to thank my parents for their unending faith and love in me, without which this would not have been possible. If it were not for the prayers and wisdom of my parents, I would not have achieved what I have now and so I dedicate this work to them.

At this point, I would also like to offer my sincere gratitude to my brother Mr. Mourya for his never-ending support and morale-boosting advice, which helped me get through some of my more challenging times.

I want to express my gratitude to all of my seniors, colleagues, and juniors for your assistance when I needed it. I want to express my gratitude to my friends for being there for me no matter what and for their unwavering support.

I also appreciate the nursing staff's and the ward staff's friendly assistance with my research. What use is a potter without clay, and what use is research without the patients' active involvement? I would like to express my sincere gratitude to each patient who consented to participate in this study, and I also want to apologize to them for any inconvenience I may have caused.

Finally, I want to congratulate myself for believing in myself and persevering in finishing my education despite difficulties.

Dr. M.V.R. Abhishek

DEDICATED TO
MY PARENTS

&
MY TEACHERS.

## **INDEX**

Sr. No.	Description	Page No.	
1.	List of abbreviations	í	
2.	List of tables	ii	
3.	List of figures	iii	
4.	Summary	iv-v	
5.	Introduction	1-2	
6.	Review of literature	3-13	
7.	Aim & objectives	14	
8.	Material and method	15-17	
9.	Observations and result	18-26	
10.	Discussion	27-29	
11.	Conclusion	30	
12.	References	31-35	
	Annexures	36-44	
	I. Ethical clearance Certificate	36	
	II. Informed consent (English)	37	
	III. Informed consent (Hindi)	38	
13.	IV. Patient information sheet (English)	39	
	V. Patient information sheet (Hindi)	40	
	VI. Data Collection Sheet	41-42	
	VII. Key to Master Chart	43	
	VIII. Master Chart	44	

# LIST OF ABBREVIATIONS

MOR	Mu Opioid Receptor	
DOR	Delta Opioid Receptor	
KOR	Kappa Opioid Receptor	
GI	Gastrointestinal	
GIRK	G protein Inward Rectifying Potassium Channels	
VTA	Ventral Tegmental Area	
DSM	Diagnostic and Statistical Manual of Mental Disorders	
SUD	Substance Use Disorder	
CBD	Common Bile Duct	
CNS	Central Nervous System	
HIV	Human Immunodeficiency Virus	
AIDS	Acquired Immuno Deficiency Syndrome	
ICU	Intensive Care Unit	
AIIMS	All India Institute of Medical Sciences	
IBM	International Business Machines Corporation	
COPD	Common Obstructive Pulmonary Disease	
RR	Relative Risk	
VAS	Visual Analogue Scale	
OUD	Opium Use Disorder	

## **LIST OF TABLES**

Table No.	Table Description	Page No.
1	Criteria according to DSM V	7
2	The Clavien Dindo scoring system of surgical complications.	10
3	Postoperative outcomes in patients undergoing non abdominal procedures.	24
4	VAS score at 24 hours in various procedures in patients with OUD vs without OUD	25
5	Comparison of post operative stay in different surgical groups	26
6	Comparison of post operative day of return of bowel sounds in different surgical groups.	

# LIST OF FIGURES

Figure	Figure Description	
No.	Figure Description	Page No.
1	Pie diagram showing frequency of opioid use disorder in the study cohort.	
2	Graphical representation of age distribution of opioid users	18
3	Graphical comparison of locality of patients	19
4	Graphical representation of age of initiation of opium	19
5	Pie diagram depicting the reason for initiation of opioids	20
6	Bar diagram depicting the type of opioid consumed	20
7	Pie diagram depicting timing of surgery in opioid users.	21
8	Graphical representation of type of surgery performed in opioid users.	21
9	Graphical representation of type of surgery performed in non-opioids.	22
10	Graphical representation of grade wise incidence of complications in the two groups undergoing exploratory laparotomy	23
11	Stacked bar diagram representing post operative outcomes in patients undergoing exploratory laparotomy	23
12	Box whisker plot for VAS score of patients undergoing exploratory laparotomy	25

## **SUMMARY**

#### Background:

Opioid use is a growing health concern in several nations across the globe. The western part of Rajasthan is known for opioid use in its raw forms as part of cultural practices. The aim of this study was to understand how the presence of opium use in preoperative period effects the postoperative outcomes.

#### Objectives:

The primary objective of this study was to compare post operative complications between patients with and without opium use disorder. The secondary objective was to compare post operative pain control and length of post operative stay between the two groups.

#### Methods:

This was a single institution based prospective cohort study conducted from January 2021 to December 2022. A total of 162 patients were included in our study after taking ethical approval and consent. The patients were divided in two groups i.e., those with Opium Use Disorder and without Opium Use Disorder based on DSM-5 criteria. Data was collected regarding age of initiation, type of opioid used, cause of initiation. Post operative complications were recorded according to Clavien Dindo Classification. Post operative pain control was assessed at 24 hours of surgery by VAS score. Comparison was done between the two groups to identify association between opioid use and severity of post operative complications, pain control and length of hospital stay.

#### Results:

Among the 162 who were recruited for the study, 68 patients (42%) had Opium Use Disorder. There was significant association between pre operative opioid use and incidence of major complications (Relative risk of 3.1 with 95% confidence interval, p value 0.016) in patients undergoing laparotomy. Pain scores were significantly higher in laparotomies (median VAS 8 in opioids vs 4 in non-opioids, 95% confidence interval, p<0.001), laparoscopic surgeries (VAS 6 vs 2, p<0.001) and other miscellaneous procedures (VAS score 8 in opioids vs 5 in non-opioids, P = 0.003). There was no significant increase in length of post operative stay in patients with Opioid Use Disorder (p value greater than 0.05).

#### Conclusion:

Consumption of raw opium in the form of Amal, Doda is still a public concern in western parts of Rajasthan. Presence of Opium Use Disorder in preoperative period causes significant increase in incidence of post operative complications. It is also associated with poor pain control and increased chances of ileus in the post operative period which further complicates the management. Substance use is a potential modifiable risk factor which needs focus to improve peri operative care and outcomes of patients.



## INTRODUCTION

Since eternal times, use of various psychoactive substances exists in the world. Further research on the biological and pharmacological effect of these substances had resulted in development of multiple derivatives for therapeutic use. Abuse and addiction to these substances has become a serious global phenomenon. Substance abuse is a complex and multifaceted problem resulting from interaction between the individual, the drug, and the community.

Opioids had evolved as a cornerstone in effective pain management over the past few decades. They are derived from opium poppy plant Papaver somniferum. The latex produced from unripe seed capsule of the plant contains alkaloids such as morphine, codeine and thebaine which are utilised for mass production of therapeutic drugs. It is further processed to heroin which is used for illegal drug trade. Overall, they can be classified into three different sub categories: (a) Opium, which includes Doda, Amal, Phukki, poppy husk, (b) Heroin which includes brown sugar and smack, (c) Pharmaceutical opioids.

One out of twenty-five individuals in United States uses a prescription opioid medication. Around nine million individuals were prescribed therapeutic opioid medication in America in 2009, and hydrocodone was the most prescribed. (1) The Centre for Disease Control and Prevention cited opioid associated morbidity and mortality as a major public concern. Despite this, opioid consumption rose by 500% between 1999 and 2011.(1) This epidemic had extended beyond American shores and high opioid related mortality is reported in Canada(2), United Kingdom (3), Australia (4), Mexico.

The National Survey on magnitude of substance use in 2019 showed that opioid use in our country is three times the global average. (5) The prevalence of opioid use is about 2.1% in India. (5) In contrast to developed countries, opioid epidemic in India is not physician induced yet. Heroin is the most commonly used opioid, followed by pharmaceutical opioids and opium. (6)

The western part of Rajasthan state is unique in its characteristics of opioid consumption. Opioid derivatives in the form of Amal, Doda are the most common cause of opioid addiction in this region. Another exclusive feature is the initiation of opium as a part of cultural and social customs making this home to largest number of non-heroin and non-prescription opioid addicts. (7)

Opioid use is associated with multiple adverse effects like respiratory depression, nervous system depression, constipation and bladder dysfunction.(8) Chronic opioid users develop changes in signalling pathways of nervous system for appreciation of reward, impulse and motivation. These changes lead to dependence and tolerance. (8)(9)(10) Changes in pain thresholds leads to challenges in pain management and rehabilitation following surgery. Patients might also report opioid induced hyperalgesia.(10) Chronic opium use was also reported to increase the risk of hepatic and pulmonary damage. (11)

Studies in orthopaedic population showed that preoperative opioid use had been associated with poor post operative pain control, decreased quality of life and increased hospital expenditures. (12) (13)(14) Various studies reported unclear outcomes results in patients undergoing cardiovascular surgeries. (15) (16)

However, limited retrospective studies which were conducted in opioid users undergoing abdomino pelvic procedures revealed increased peri operative morbidity, readmission rates and healthcare utilization and expenditures. (17) (18) (19)

The indigenous opioid derivates of western Rajasthan, despite having lesser concentrations of opioid alkaloids, may result in significant morbidities due to high quantities of consumption. Our study was aimed at understanding the pattern of opioid abuse and its effects on post operative outcomes of such patients.



# REVIEW OF LITERATURE



## REVIEW OF LITERATURE

The word Opium was derived from the Greek term "opos," which means juice, signifying that natural opiates are derived from the latex or resin of the plant *Papaver somniferum*. Analgesic use of opioid substances had been scripted since 300 B.C. Any substance with similar functional and pharmacological properties is called an opioid. Numerous synthetic opioids had been created since opium and codeine were first chemically separated 200 years ago and opioid receptors were cloned in the 1990s. Endorphins, enkephalins, dynorphins are some naturally occurring ligands for opioid receptors. (20)

There are three classes of opioid receptors – MOR (mu opioid receptor), DOR (delta opioid receptor), KOR (kappa opioid receptor) which belong to rhodopsin family. (20) The biological effect of opioid depends upon the receptor, the downstream intracellular messenger system and the ion channels that regulate them. All the three types of receptors are G protein type which are linked and coupled to secondary messenger - cyclic adenosine monophosphate (cAMP) and inward rectifying potassium channels (GIRK). Activation of GIRK causes hyperpolarisation and inhibition of activation potentials. Thus, opioids inhibit activity of several neurons causing analgesia and sedation. (20)

Effects of opioids are related to neuroanatomic location of mu receptors. Activation of mesolimbic dopaminergic pathways from ventral tegmental area (VTA) to the nucleus accumbens produces Euphoric effect. This is caused by inhibition of GABAergic neurons. Large bolus doses of opioids produce a burst of dopamine neuron activity which produces the so called "high" by misused substances. However, transdermal and oral routes of prescription opioids do not cause such effect due to slow release. Normal mu-receptor activation by endogenous opioids inhibits the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA)-cAMP response-element binding protein (CREB) cascade in noradrenergic neurons within the locus coeruleus through inhibitory Gi/o protein influence on adenylyl cyclase. Similarly, acute exposure to opioids inhibits this system, whereas chronic exposure to opiates leads to upregulation of the cAMP pathway in an attempt to oppose opioid-induced inhibitory influence. Upregulation of this system is involved in opioid tolerance, and when the opioid is removed, unopposed noradrenergic neurotransmission is involved in opioid withdrawal. Upregulated PKA phosphorylates CREB, initiating the expression of various genes such as

tyrosine hydroxylase (TH) and brain-derived neurotrophic factor (BDNF). BDNF is implicated in long-term neuroplastic changes in response to chronic opioids. (21)

## Development of opioid tolerance and withdrawal (22):

The development of tolerance and withdrawal was linked to mu receptors and the following cAMP – protein kinase A – CREB (CAMP response element binding protein) intracellular cascade. Functional polymorphisms in the mu receptor gene, epigenetic methylation leading to changes in DNA region of mu receptor gene are responsible for difference in abuse liability of individuals. When large doses of opioids saturate the mu receptors and cause inhibitory effect over weeks, changes occur in a second set of neurons in the locus cereleus leading to tolerance and withdrawal symptoms.

#### Opioid derivatives (22):

Most clinically used opioid agonists act on MORs. They are responsible for analgesia, changes in respiratory, cardiovascular, gastrointestinal and neuroendocrine functions. The milky juice extracted from unripe seed capsules of the opium poppy plant is dried and powdered to make several alkaloids. They are basically divided into two classes. Phenanthrenes are morphine, codeine and thebaine. Benzylisoquinolines are papaverine and noscapine.

Many synthetic derivatives are simple modifications of morphine or thebaine. Thebaine has poor analgesic effect but its derivatives etorphine are highly potent. Oxycodone and naloxone are also derived from thebaine. Hydromorphone, oxymorphone and oxycodone are derived from morphine molecule. Heroin is diacetylmorphine which rapidly gets hydrolyzed into 6-Mono acetyl morphine, a highly lipid soluble agent which is responsible for the pharmacological actions of heroin.

#### **Problem statement**

Opioid analgesics were historically used for acute and cancer related pain. Early publications showing lower rate of addiction to opioids led to surge in utilization of opioids in chronic non-cancerous pain. (23) (24) Consumption of opiates and its misuse in United states had reached epidemic status in the last two decades. Over nine million individuals in the United States reported use of opioids with hydrocodone alone prescribed 130 million times in 2009.(17) Similar monumental increase had been documented in Canada, Australia and Mexico.

#### Trend in Indian subcontinent:

Two national surveys were held in 2004 and 2019 to estimate the magnitude of substance use in India. The 2019 survey estimated the prevalence of opioid use to be three times the global average at 2.06%, heroin (1.14%) being the most commonly used followed by pharmaceutical opioids(0.96) and other forms of opium(0.52%). An estimated 77 lakh "problem opioid users" were present in the country. Uttar Pradesh, Punjab, Haryana, Delhi were the leading states of opioid use .(25)

India is one of the twelve countries that were allowed poppy cultivation following International conventions.(26)The Narcotics and Psychotropic Substances Act, 1985 empowers the government to regulate the cultivation of opium. (6) In order to facilitate access to essential prescription opioids, India's previously stringent National Drugs and Psychotropic Substances Act was amended in 2014. These include fentanyl, hydrocodone, codeine, which were prominent cause of the epidemic in America. According to 2004 census, the non-synthetic form of opium was the most consumed type in our country. The 2019 national survey showed shift to heroin as the most common opioid used.(6) These trends indicate the chances of pharmaceutical opioid epidemic in the coming decade similar to western countries.

Rajasthan houses one the highest number of traditional opium users in the country. Because of centuries-old sociocultural practices, the western districts of Rajasthan, known for their desert climate, bear a disproportionate burden of opioid users. Opium is available in the local communities in two forms. Amal, which is the nugget form, is dissolved in water and filtered through a porous cloth. The extract is then consumed in liquid form. Doda, on the other hand is a powder form which is mixed with dried cow dung and smoked through a pipe. (7) (27)

Consumption of Amal or Doda often starts at a young age due to exposure to it in social gatherings. They initially start it as a fun during social gatherings or festivals or to enhance their status in society. Later, it converts into a habit to alleviate worries during dry seasons or pain due to strenuous work. The ancient Rajput clan particularly used this to reduce bleeding and apprehension during wars. The population also believe that opium mitigates many health problems like cough, diarrhea, body aches. It was also believed to improve cardiac functioning and also as an aphrodisiac .(7)

To handle this huge burden, state government regulated the sale of poppy straw through licensed shops called Doda post. In 2016, Rajasthan high court cancelled the permits of all

Doda posts. Even after the ban, there was no significant reduction in the number of opioid users due to illicit trade. (26)

#### Opioid use disorder:

The terms dependence and addiction, which were used in classification given by Diagnostic and Statistical Manual of Mental Disorders (DSM) IV became obsolete in 2013 with the introduction of DSM -5 edition. The revision brought numerous changes in organization and diagnostic criteria of nearly all the mental disorders described previously. The latest edition includes opioid use disorder, opioid intoxication and opioid withdrawal under opioid related disorders. (28)

A major change in this classification is merging "substance abuse" and "substance dependence" under a single terminology i.e., Substance Use Disorder (SUD). According to DSM-5, the diagnosis of opioid use disorder requires use of opioids and fulfilling two or more of eleven criteria in a twelve-month period. (29) Diagnostic criteria is mentioned in the Table 1 below. Withdrawal symptoms include dysmorphic mood, nausea, vomiting, muscle aches, rhinorrhea, lacrimation, fever, yawning, pupillary dilation, piloerection, diarrhea and insomnia. (22)

Table 1: The DSM 5 criteria.

#### DSM 5

# Criteria "SUD": Two out of 11 criteria clustering in a 12-month period are needed to

- · Recurrent substance use in situations where it is physically hazardous
- · Recurrent substance use resulting in a failure to fulfil major role obligations at
- · Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance

Added: Craving or a strong desire or urge to use the substance

- Substance is taken in larger amounts or over a longer period than was intended
- · There is a persistent desire or unsuccessful efforts to cut down or control substance use
- · A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
- · Important social, occupational, or recreational activities are given up or reduced because of substance use
- · Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by substance use
- · Tolerance, as defined by either:
- 1. a need for markedly increased amounts of substance to achieve intoxication or desired effect or
- 2. a markedly diminished effect with continued use of the same amount of the substance
- · Withdrawal which is manifested by either:
- 1. the characteristic withdrawal syndrome for the substance
- 2. the substance (or a similar substance) is taken to relieve or avoid withdrawal symptoms

Severity | Severity is assessed in terms of the number of symptoms that meet criteria:

- Mild: two to three symptoms
- Moderate: four to five symptoms

Severe: six or more symptoms

# Systemic effect of opioid misuse:

Inhalational and intravenous opioids cause high drug concentrations in brain, that produces "rush" which is followed by euphoria, tranquility and sleepiness. Besides the effects on central and peripheral nervous system, they also effect wide range of other organs. Secretion of pituitary hormones such as corticotropin releasing factor and luteinizing hormone is reduced which in turn reduces levels of cortisol and sex hormones respectively. This causes impaired stress response and reduced libido. They also effect secretion of thyrotropin and growth hormone. They cause reduction in sensitivity of brainstem to stimuli like increased blood carbon dioxide levels. This can lead to respiratory depression and in patients with pulmonary disease, may lead to significant complications. Loss of gag reflux may cause aspiration pneumonitis. Death from opioid poisoning in majority of cases is due to respiratory arrest.

Opioid receptors are richly distributed along the gastrointestinal tract. Opioids cause increase in basal tone of gut muscles causing non propulsive contractions. This causes delayed gastric emptying, reduced small bowel motility leading to constipation. Direct stimulation of chemoreceptor trigger zone in area postrema of medulla causes nausea and vomiting. They cause sphincter of Oddi constriction leading to biliary colic and dilatation of CBD.

High doses of opioid can cause hypotension by release of histamine from mast cells, inhibition of baroreflexes and reduced cardiac activity. Concurrent use of CNS depressants can increase the risk of hypotension. Higher doses can increase skeletal muscle tone and cause effects ranging from twitching to generalized spasm. Chronic opioid use can increase sphincter tone and urinary stasis in postoperative period.

Chronic opioid use can lead to opioid induced hyperalgesia. Though the exact mechanism is not well understood, few suggested that the stimulatory effects on innate immune signaling leads to central sensitization. Opioids also modulate immune system by directly effecting cells of immune system or through central neuronal mechanisms. This leads to modest immunosuppression and increased susceptibility to infections.

Intravenous opioid users have separate risk of complications. Sharing of syringes and needles increase the chance Hepatitis B, HIV/AIDS. Injections can also cause abscesses in various organs, meningitis and osteomyelitis. (22)

## Post operative complications:

Irrespective of years of training and experience, every surgeon faces surgical complications. They can occur due to various reasons: (a) due to compromise of patient's condition by disease process; (b) due to technical errors in the procedure; (c) due to general condition of patient and associated comorbidities and addictions.(30) Evaluation of surgical procedures in previous centuries was hampered due to lack of consensus to define and grade the surgical outcomes. Initial classifications included inconsistent use of terms like minor, moderate and major.(31)

#### Clavien - Dindo grading system:

A novel approach was developed to rank complications by Clavien et al in 1992. Based on the outcome, they were differentiated into (a) complication, (b) failure to cure and (c) sequela. Complications were defined as unexpected events not intrinsic to procedure. When the purpose of the procedure was not fulfilled, it was termed as failure and outcomes inherent to procedure were termed as sequela. (31)

These complications were classified into four grades:

- Grade 1: These are alterations from the ideal postoperative course, non-lifethreatening, and with no disability.
- Grade 2: Potentially life-threatening but without residual disability. These are again subdivided based on the requirement for invasive procedures.
- Grade 3: Those with a residual disability, including organ resection or persistence of life-threatening conditions.
- Grade 4: Death as a result of complications.

After 12 years of its routine usage, it was modified in 2004. This was based on therapy required to treat the complication. The rationale was to eliminate the subjective interpretation of serious adverse events. A 5-scale classification system was created as shown in the Figure 2 below. It was validated in a cohort study with 6336 participants. The reproducibility was evaluated by international surveys and the current scoring system had been used for the past 25 years. Some institutions further categorized them into minor complications (includes grade I and grade II) and major complications (includes grade III to grade V). (32) (33)

Table 2: The Clavien Dindo Scoring system of surgical complications.

## **Classification of Surgical Complications**

Definition
Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are drugs as antiemetics, antipyretics analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside Requiring pharmacological treatment with drugs other than such
allowed for grade I complications Blood transfusions and total
parenteral nutrition are also included
Requiring surgical, endoscopic or radiological intervention
Intervention not under general anaesthesia
Intervention under general anaesthesia
Life-threatening complication (including CNS complications)* requiring IC/ICU management
Single organ dysfunction (including dialysis)
Multiorgan dysfunction
Death of a patient
If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

<sup>\*</sup>Brain haemorrhage, ischemic stroke, subarachnoid bleeding, but excluding transient ischemic attacks.

IC- Intermediate care; ICU-Intensive care unit

Patients undergoing emergency surgery differ significantly from those having elective procedure. Patients undergoing emergency procedures do not have the phase of pre operative optimization. A fraction of patients present with organ failure in pre operative period. Panu et al. conducted a cohort study on 444 patients having emergency surgical procedure. They had come to a conclusion that Clavien Dindo classification can be applied for evaluation of emergency procedure outcomes with consideration of risk stratification of patient's comorbidities and preoperative organ dysfunction. (34)

## PREVIOUS STUDIES

Malviya A et al., (2011) performed a prospective study which included cohorts of 71 opium addict and 50 non-addict patients admitted in various surgical wards. The study focused on presentation and the post-surgical complications encountered in these patients vis-à-vis others. The work concludes that opium addicts suffer a much higher degree of postoperative morbidity as compared to non-addicts. They have found the occurrence of respiratory complications in opium addicts as 50% as compared to 24% in non-opium addicts. (19)

Cron et al., (2017) conducted a retrospective analysis of effect of preoperative opioid use on hospital costs and outcomes after major abdominal surgeries. The study showed 9.2% higher hospital costs in opioid users. Pre operative opioid use was also associated with longer length of stay (95% CI 2.3%–23.5%; adjusted means 5.9 vs 5.2 days; P ¼ 0.015), increased risk of major complications (odds ratio 1.36; 95% CI 1.04–1.78; adjusted rates 20% vs 16%; P ¼ 0.023) and readmissions (odds ratio 1.57; 95% CI 1.08–2.29; P ¼ 0.018). (17)

Walijee et al., (2017) had done a retrospective study on Effect of Preoperative Opioid Exposure on Healthcare Utilization and Expenditures Following Elective Abdominal Surgery in United States. They observed that perioperative morbidity, readmission rates, and costs were higher among patients who reported preoperative opioid use. However, post-operative complications, use of analgesia were not assessed. (18)

Menendez et al., conducted a retrospective cross-sectional study based on data from National Inpatient Sample (NIS) of United States from 2002 to 2011 to assess the prevalence of opioid abuse and its effects on post operative mortality and morbidity in elective orthopaedic surgery cases. It showed a 152% raise in prevalence of opioid use over the decade. The study also showed strong association of opioid abuse with postoperative mortality (odds ratio 3.7: 95% CI, 2.7-5.1), increase in post operative complication like surgical site infection (OR, 2.5; 95% CI, 2.0-3.0), pneumonia (OR, 2.1; 95% CI, 1.8-2.3) and postoperative ileus (OR, 1.4; 95% CI, 1.3-1.6). (12)

Lee et al ., conducted a prospective cohort study to identify pre operative opioid use as a predictor of post operative outcome in patients who were undergoing spine surgery. Evaluation of 583 patients revealed that preoperative opioid use had increased scores of post operative disability indices. (35)

Ayumi et al., conducted a retrospective analysis on opioid abuse and its association with obstetrical outcomes in pregnant women. Data of over 37 million deliveries from 1998 to

2011 in National Inpatient sample database was analysed. It showed increased odds of maternal death(adjusted odds ratio [aOR], 4.6; 95% CI, 1.8 to 12.1,) and other obstetrical complications like Intra uterine growth retardation (aOR, 2.7; 95% CI), Placental abruption, length of stay (aOR, 2.2; 95% CI). (36)

Gary M et al., conducted retrospective cohort study to analyse the impact of opioid use disorder on hospital costs and length of stay in postoperative patients. It revealed significant increase in total hospital costs (7.4% increase; 95% CI 3.83 to 10.96; p < 0.001) and length of stay (10.3% increase; 95% CI 6.5 to 14.2; p < 0.001) in patients with opioid use disorder.(37)

Azarasa et al., (2009) had done a prospective study to investigate the prevalence of substance use and its effects on postoperative morbidity and mortality among patients undergoing cardiac surgery in northwest Iran. According to this study, postoperative complications and in hospital mortality in opioid users were not statistically different from control groups (38).

**Dewan et al.**, conducted a retrospective cohort study on 5.7 million adults to compare outcomes in cardiac surgery between patients with and without OUD. It showed that mortality was similar between both the groups (3.1% in OUD vs 4.0% in without OUD: P = 0.12). However, the overall incidence of major complications was higher in the opioid use group (7.3% vs 3.8%: P<0.001). It was also associated with a longer length of stay and higher hospital costs. (39)

Sadeghian et al., conducted a retrospective cohort study on 4398 patients to identify association between opium dependence and post operative complications following coronary bypass procedure. A propensity matched study revealed no significant relation with in hospital complications. (15)

Safaii et al., conducted a descriptive study to compare morbidity and in hospital mortality in patients undergoing coronary bypass procedure. It showed no significant difference in mortality or postoperative length of stay between opioid users and non-users. However, rehospitalisation rates were higher in opioid users. (16)

Margaret et al., study on how new persistent opioid use in patients after bariatric surgery effects physiological and psychological outcomes. In a total of 27,799 patients who underwent bariatric surgery over 10 years, incidence of new persistent opioid use was 6.3%. The study showed that new opioid users had poorer surgical success rates (57.6% vs.

60.3%; p < 0.0001) and worse scores in psychological wellbeing (35.0 vs. 33.1; p < 0.0001) and depression (2.4 vs. 5.0; p < 0.0001). (40)

Effect of preoperative opioid use on post operative outcomes had been studied in several retrospective studies in orthopaedic and cardiac surgeries. However, its effect on abdominal surgeries has not been widely explored. Given the effect of opioid derivatives on various organ systems, we aim to understand its impact in outcomes of general surgery patients. This can further help for surgical quality improvement by creating tailored peri operative care in such patients. Despite being less potent, the high burden of native, non synthetic opioid consumption in the country necessitates further research to understand their role in postoperative outcome.



# AIM & OBJECTIVES



#### AIM AND OBJECTIVES

#### AIM:

To determine association between opium use disorder and post-operative complications.

#### **OBJECTIVES:**

- Primary objective:
- To compare post-operative complications between operated patients with opium use disorder and without opium use disorder.
- Secondary objective:
- To compare post operative pain control in patients with and without opium use disorder.
- To compare length of post operative stay in patients with and without opium use disorder.



#### MATERIAL AND METHODS

## 1. STUDY SETTING

This study was conducted in patients admitted under General Surgery department of All India Institute of Medical Sciences (AIIMS), Jodhpur.

## 2. STUDY DESIGN

A hospital based prospective cohort study.

## 3. STUDY PARTICIPANTS

## Inclusion Criteria:

All patients admitted under general surgery department who underwent surgery.

**Exclusion Criteria:** Patients with either of the following conditions were completely excluded from the study.

- 1. Patients who were above 70 years age.
- 2. Patients who required ICU care pre operatively.

#### 4. SAMPLE SIZE

This study recruited 162 adult patients who had been admitted and operated in the Department Of General Surgery, All India Institute of Medical Sciences, Jodhpur.

Malviya et al (2011) performed a prospective study which included cohorts of 71 opium addict and 50 non-addict patients admitted in various surgical wards. They have found the occurrence of respiratory complications in opium addicts as 50% as compared to 24% in non-opium addicts. We estimated the above sample size at 80% power, 95% confidence interval, 10% contingency.

#### 5. STUDY DURATION

The patients were enrolled from January 2021 to June 2022, and the next 6 months (1<sup>st</sup> July 2022 to 31<sup>st</sup> December 2022) were used for data compilation, data analysis, and submission of the final draft.

### 6. STUDY PROCEDURE

After receiving approval from the institutional research committee and the institutional ethics committee, the hospital-based prospective cohort study was carried out in the Department of General Surgery at AIIMS, Jodhpur.

All the patients admitted in the department of General Surgery had a thorough history taking as a part of routine clinical care. Patients undergoing surgery were explained in detail about the format of the study with the help of a patient information sheet. A written and informed consent was taken from patients who were willing to participate in the study. These patients were considered as our study cohort. Patients were diagnosed with OUD if they fulfilled at least two out of eleven criteria given by DSM-5 for substance use disorder.

Rest of the operated patients were considered not to have Opium Use Disorder (non-OUD group).

Demographic data including age, gender, place of living, religion was collected. Data regarding comorbidities, substance use was collected. Patients with opioid use disorder were inquired about the age of initiation, frequency of usage, form of opium intake and reason for initiation.

All the patients in the cohort were followed up through the peri operative period till discharge. Post operative pain control was evaluated with the help of Visual Analogue Scale at 24 hours of post operative period. Duration of hospital stay following surgery was recorded in days. Complications in the post operative period were documented and classified according to Clavien Dindo grading of post operative complications. Care was taken not to include existing pre operative organ failure as a post operative complication. Day of return of bowel sounds was noted by auscultation. All the patients in the cohort were classified into two groups: with OUD and without OUD. Further data analysis was compared between the two groups. The primary and secondary objectives were analysed between patients undergoing similar kind of procedures by grouping them into three categories viz. exploratory laparotomy, laparoscopic and other (includes debridement and amputations).

#### 7. STATISTICAL ANALYSIS

Data were analysed using Statistical Package for Social Sciences (SPSS) version (28.0), IBM Inc.

Descriptive statistics such as mean, median, standard deviation and interquartile range for continuous variables and frequency along with percentages of categorical variables were calculated.

Summarized data were represented using Graphs and Tables. Student t-test was used for comparison of quantitative data with normal distribution. Mann Whitney U test was used to compare numerical data without normal distribution, and two-tailed Chi square analysis was used for categorical data.

Multiple groups of continuous data were compared using a Kruskal-Walli's test.

The Wald H0 test was used for categorical data. A p-value of <0.05 was taken as significant.

#### 8. ETHICAL CONSIDERATION

The Institutional Ethics Committee (IEC) granted ethical approval (AIIMS/IEC/2021/3362). After obtaining written consent, patients were recruited. All patients recruited in the study received standard treatment care and were assured that their recruitment in the study did not alter their standard diagnostic evaluation and management.

All personal information gathered throughout the study was kept strictly confidential.



# OBSERVATIONS & RESULTS



#### **OBSERVATIONS AND RESULTS**

#### Study cohort:

During the period of investigation, a total of 162 patients were recruited out of which 68 patients (42%) had OUD and 94 (58%) patients did not have OUD.

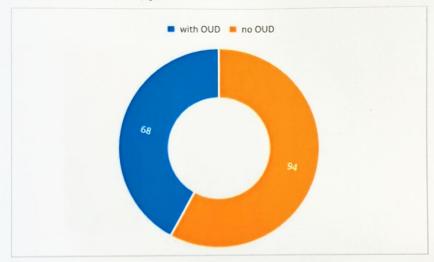


Figure 1: Pie diagram showing frequency of opioid use disorder in the study cohort.

#### Demographic characteristics of patients with OUD:

In our exposure group, 65(95.6%) patients were male and 3 patients (4.4%) were females. They were aged between 32 and 70 years with a median age 60 years (IQR = 65 to 47) as shown in figure 2.



Figure 2: Graphical representation of age distribution of OUD group.

In our study, 75% of the patients in the exposure group (n = 51) belonged to rural areas of Rajasthan and 25% belonged to urban areas as shown in figure 3. Whereas, 73.4% of non OUD patients belonged to rural areas and 26.5% to urban areas. 95.6% of the patients (n = 65) were Hindus and 4.4% (n = 3) were Muslims.

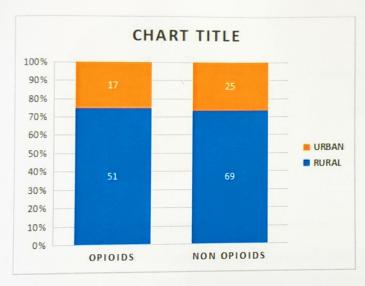


Figure 3: Graphical comparison of locality of cohort.

The mean age of initiation of opium was 32.6 years ranging from beginning at as early as 20 years till 64 years as shown in figure 4.

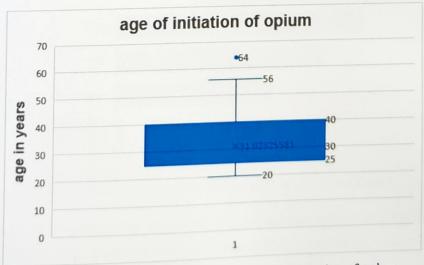


Figure 4: Graphical representation of age of initiation of opium.

It was observed that 22.4% patients started opioid use due to social customs. Others started opioid use either for pain relief (32.8%) or out of own interest (44.8%).

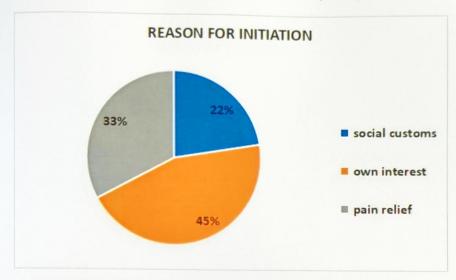


Figure 5: Pie diagram depicting the reason for initiation of opioids

The form of opium abuse was also different with 33.8% patients using only Doda, 25% patients using Amal/Afeem and the rest (39%) in combination as shown in figure 6. 62 (95.8%) patients consumed opium on a daily basis and the rest (4.2%) on a weekly basis. 29 patients (42.6%) also had history of consumption of smoking, alcohol or some other form of substance.

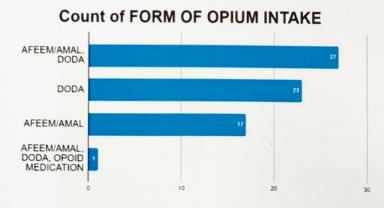


Figure 6: Bar diagram depicting the type of opioid consumed.

In our study, 36.7% patients had associated comorbidities like hypertension (22%), Type 2 Diabetes Mellitus (1%), peripheral vascular disease (8.8%), malignancy (7.4%) and Chronic Obstructive Pulmonary Disease (COPD) (2.9%).

Twenty five percent of patients with OUD (n = 17) underwent elective surgical procedure whereas 75% (n = 51) patients underwent surgery on emergency basis as shown in figure 7.

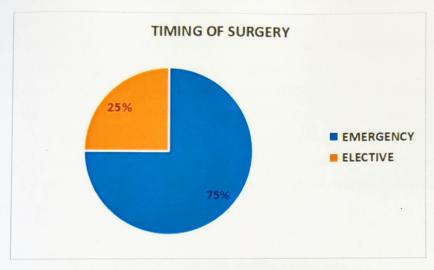


Figure 7: Pie diagram depicting timing of surgery in OUD group.

In our study, 54.4% patients underwent exploratory gastrointestinal (GI) procedure, 23.5% underwent laparoscopic GI procedure, 22.2% patients underwent miscellaneous procedures like amputation (5), debridement (7), Incision and drainage (2).

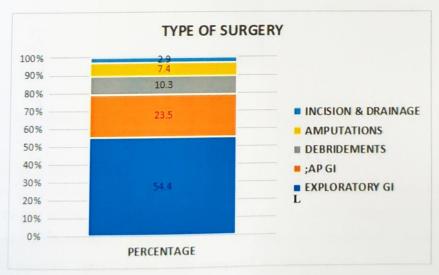


Figure 8: Graphical representation of type of surgery performed in OUD group

#### Demographic characteristics of patients without OUD:

Out of the 94 patients in the study cohort without OUD, 75 patients (79.8%) were male, 19 patients (20.2%) were female. 73.4% patients belonged to rural region and 26.6% belonged to urban region.

64.8% of patients had no history of addiction while the remaining had history of consumption of products like tobacco (28.7%), alcohol (8.5%), ganja (2.1%).

Associated comorbidities included type 2 Diabetes Mellitus in 21.2%, Hypertension in 23.4%, Peripheral vascular disease in 9.5% and malignancy in 3.1% of patients.

94.7% (n=89) patients underwent emergency surgical procedures and 5.3% underwent elective procedures. These included exploratory GI surgeries (69.1%), laparoscopic surgeries (10.6%) and other procedures like amputations (14.9%) and debridement (4.3%) as shown in figure 9.

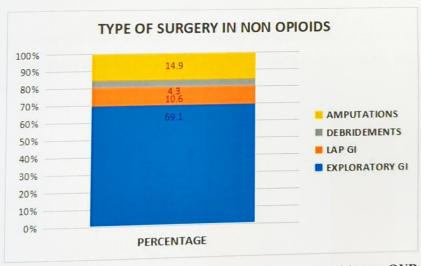


Figure 9: Graphical representation of type of surgery performed in non OUD group.

#### Post operative complications:

In our study, out of 98 patients who underwent exploratory laparotomy (37 with OUD vs 65 without OUD), 89.2% of patients with OUD and 55.4% of patients without OUD developed post operative complications. Hence, patients with opium use disorder were more likely to have post operative complications when compared to others.  $X^2$  (2, N=102) = 12.3, p = 0.0004.

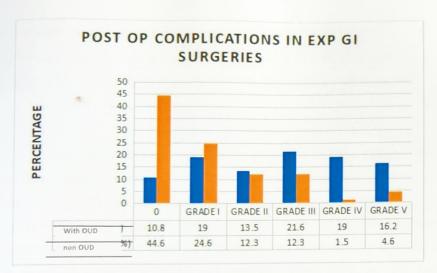


Figure 10: Graphical representation of grade wise incidence of complications in the two groups undergoing exploratory laparotomy.

Our study showed that there was significant association between risk of major complications (Clavien Dindo grade III, IV,V) in patients with opioid use disorder.  $X^2$  (2,N= 102) = 19.9, p value < 0.01.

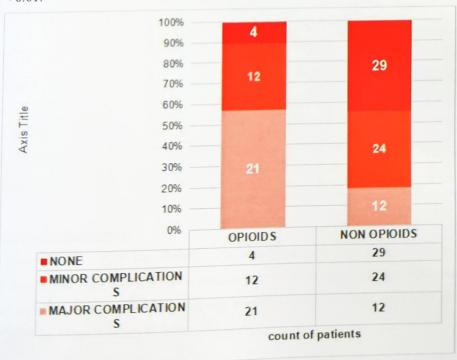


Figure 11: Stacked bar diagram representing post operative outcomes in patients undergoing exploratory laparotomy.

Incidence of major complications in OUD group= 21/(12+4+21) = 0.56Incidence of major complication in non OUD group = 12/(29+24+12) = 0.18Relative Risk (RR) = incidence in pts with OUD / incidence in pts without OUD = 3.1 (p value = 0.016)

A total of 26 patients underwent laparoscopic procedure. 37.5% patients with OUD developed minor complications and 12.5% developed major complications. However, all the 10 patients without OUD were discharged free of post operative complications.

34 patients in cohort group underwent various miscellaneous procedures like amputation and debridement. It was found that there was no significant difference in incidence of post operative complications between OUD and non-OUD group,  $X^2(2, N=34)=1.5$ , p = 0.21.(shown in Table 3)

Table 3: Depicting postoperative outcomes in patients undergoing non abdominal procedures.

	OUD present?							
		no	yes					
	Count	percentage	Count	percentage				
0	6	31.6%	2	13.3%				
GRADE I	4	21.1%	4	26.7%				
GRADE II	0	0.0%	1	6.7%				
GRADE III	8	42.1%	4	26.7%				
GRADE IV	1	5.3%	3	20.0%				
GRADE V	0	0.0%	1	6.7%				

#### Post operative pain control:

It was observed that opium use disorder was associated with poor analgesic control and significantly higher pain scores when compared to non OUD group. Median VAS scores at 24 hours in exploratory laparotomy group was 8 in OUD group and 4 in non OUD group (p value <0.001 by Mann Whitney U test).

Table 4: Depicting VAS score at 24hours in various procedures in patients with OUD vs without OUD

	opiu	m us	e diso	rder prese	ent?		
VAS score at 24 hours	n	ye	p value				
	Median	Q1	Q3	Median	Q1	Q3	
<b>Exploratory Laparotomy</b>	4.0	4.0	4.0	8.0	6.0	8.0	< 0.001
Laparoscopic surgery	2.0	2.0	2.0	6.0	5.5	7.5	< 0.001
others	5.0	4.0	6.0	8.0	6.0	8.0	0.003

<sup>\*</sup>Q1 = first quartile, Q3 = third quartile

Median VAS score at 24 hours in laparoscopic group was 6 in OUD group and 2 in non-OUD group (P value <0.001 by Mann Whitney U test). Median VAS scores in patients who underwent miscellaneous procedures was 8 in OUD group and 5 in non-OUD group. (p value 0.03)

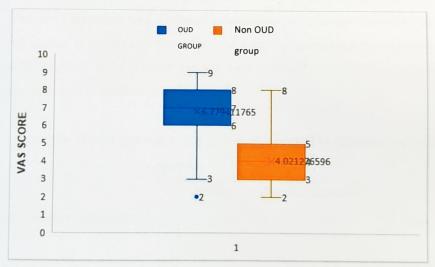


Figure 12: box whisker plot for VAS score of patients undergoing exploratory laparotomy.

#### Length of post operative hospital stay:

In our study, no significant association was found between presence of opioid use disorder and length of post operative stay irrespective of type of procedure done.

Table No 5: Comparison of post operative stay in different surgical groups.

	opiu	m us	e disc	order pre	sen	t?	
Length of post operative stay (days)	no			yes			p value
	Median	Q1	Q3	Median	Q1	Q3	
<b>Exploratory Laparotomy</b>	7.0	6.0	11.0	11.0	7.0	14.0	0.051
Laparoscopic surgery	3.0	2.0	3.0	4.0	2.5	6.5	0.097
others	7.0	4.0	12.0	9.0	7.0	16.0	0.286

<sup>\*\*</sup> P value calculated by Mann Whitney U test \*Q1 = first quartile, Q3 = third quartile

#### Post operative Ileus:

It was observed that the risk of post operative ileus was significantly higher in OUD group. The median time for return of bowel sounds was significantly higher in OUD patients (3 days in exploratory laparotomy procedure and 2 days in laparoscopic procedures) when compared to non-OUD group (2 days in laparotomy procedure and 1 day in laparoscopic procedures), p value by Mann Whitney U test. Similar results were identified in laparoscopic and miscellaneous procedure group. (Shown in table 6)

Table No 6: Comparison of post operative return of bowel sounds in different surgical groups.

	opium	use	disc	order pre	sent	?	
Day of return of bowel sounds (days)	no			yes			p value**
	Median	Q1	Q3	Median	Q1	Q3	
Exploratory Laparotomy	2.0	1.0	2.5	3.0	2.0	5.0	< 0.001
Laparoscopic surgery	1.0	1.0	1.0	2.0	2.0	3.0	0.001
others	1.0	1.0	1.0	2.0	1.0	2.0	0.003

<sup>\*\*</sup> P value derived by Mann Whitney U test \*Q1 = first quartile, Q3 = third quartile







#### DISCUSSION

Compared to other major nations suffering from the ongoing opioid epidemic, our country faces a different challenge in the type of opiates consumed and the socio-cultural customs attached with it. Our study focussed on effects of opium use disorder on surgical outcomes of patients.

A total of 68 patients had opioid use disorder in our study. 95.6% of these patients were male. Malviya et al reported an all-male series in their study. (19) However, ethnographic study by Ganguly (7) described prevalence of opium use even in females during social gatherings. Adults of both the sexes believe that opium mitigates several health problems. The low reported female prevalence may be due to associated social stigma.

Seventy five percent of opioid users in our study belonged to rural parts of Rajasthan, indicating high prevalence of opium use in the village areas. People living in desert regions of western Rajasthan started using opium to alleviate pain during wars and to escape mental stress during drought seasons. (11) Lack of adequate health care system in the desert regions even in this century encouraged the locals to continue their traditional practices. Studies show prevalence rate of opium addicts as high as 13.4% in western Rajasthan villages with highest prevalence in Barmer district at around 8.4%. (41) (11)

The exclusive feature in this part of Indian subcontinent is the initiation of opium as a part of social customs. It was mandatory in few regions to consume opium in social gatherings and weddings. This had led to exposure to the drug at young age group. (7) The mean age of initiation of opium in our study was 32.6 years starting at as early as 20 years our age. Malviya(19), who did a similar study had their youngest opium addict of 30 years. Our study showed that nearly 45% patients started opioid use out of own interest and 22% due to social customs.

In contrary to worldwide trend where heroin or prescription medication is the leading type of opioid abused, Rajasthan houses the largest number of natural opioid abusers. Amal and Doda are obtained from dried opium husk. Doda is a cheaper variant which is easily available even to the poorer sections of society. Majority of patients in our study also used Doda (33.8%) as the most common single form of opioid substance.

The severity of post operative complications in our study was measured based on the type of intervention used using Clavien Dindo Classification. The rationale was to eliminate subjective interpretation of adverse events and tendency to downgrade complication. (31)

To assess the primary and secondary objectives of our study, we had identified all the

patients into three different groups based on type of procedure performed i.e., open abdominal surgeries, laparoscopic abdominal surgeries and other miscellaneous procedures. Laparotomy surgeries comprise of larger incisions and higher postoperative pain when compared to laparoscopic surgeries. They are associated with higher chances of post operative atelectasis and pleural effusion due to pain. Opioids are known to effect respiratory centres, immune system and gut motility which increase the risk of post operative complication. Our study showed that patients with OUD were three times more likely to have major complication (grade III, IV, V) than non- OUD group (RR = 3.1, p value 0.016) during open abdominal surgeries. However, no significant association was found between incidence of post operative complications and opioid use in laparoscopic or other miscellaneous surgeries. This can be also be attributed to fewer number of patients in the above two groups. Similar findings were noted by Malviya (19) and Cron et al(17) in abdominopelvic surgeries. Supporting results were also seen in studies done in orthopaedic and cardiac patients. (12) (39) However, some observational studies done in cardiac surgery patients did not show significant association between opioid abuse and operative outcomes. (15)(38)(16)

Pain management is a major challenge for the surgeon and anaesthetist in the post operative period. Tolerance to opioids and opioid induced hyperalgesia can cause difficulty in achieving adequate analgesia. (10) (8) (22) We observed that pain scores were significantly higher in patients with opioid use disorder irrespective of type of procedure performed. Poor pain control can also lead to increase in length of stay and consequent health care utilisation and expenditures. This was seen in many studies conducted on patients undergoing orthopaedic and abdominopelvic surgeries (18) (12).

In our study, length of hospital stay was not significantly increased in patients with opium use disorder. In contrast, retrospective studies conducted by Walijee et al(18) and Cron et al (17) showed longer lengths of stay in opioid users. This was attributed to higher incidence of complications, ileus and poor pain control.

### Strengths and limitations:

Many studies done previously were retrospective analysis. The major strength of our study was being a prospective type of cohort study were appropriate documentation of exposure and outcomes in the follow up period was possible. Utilisation of DSM 5 criteria helped in accurate diagnosis of Opium Use Disorder and strengthen interpretation as per of our objectives.

Our study had some shortcomings. There was no protocol for drugs to be used for initiation and step up of post operative analgesia. Occasional use of natural opioids or opioid medications in patients under non exposure group can affect the study outcomes. Effect on individual organ system was not analyzed as Clavien Dindo classification was used.



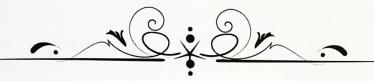
# CONCLUSION



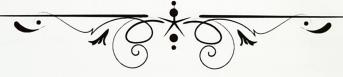
#### CONCLUSION

To conclude, hedonistic and traditional consumption of raw opium in the form of Amal, Doda is still a public concern in western parts of Rajasthan. Presence of Opium Use Disorder in preoperative period causes significant increase in incidence of post operative complications. It is also associated with poor pain control and increased chances of ileus in the post operative period which further complicates the management. All of this translates into greater utilization of hospital resources and hospital costs.

Substance use is a potentially modifiable risk factor which needs focus amid the opioid pandemic worldwide. Our study further stresses upon identification of such patients in the pre operative period which can help to improve peri operative care and outcomes.



## REFERENCES



#### REFERENCES

- Kenan K, Mack K, Paulozzi L. Trends in prescriptions for oxycodone and other commonly used opioids in the United States, 2000-2010. Open Med Peer-Rev Indep Open-Access J. 2012;6(2):e41-47.
- The Opioid Crisis: A Global Problem [Internet]. PainEDU. 2018 [cited 2022 Dec 27]. Available from: https://www.painedu.org/opioid-crisis-global-problem/
- Kopf D. The surprising geography of opioid use around the world [Internet]. Quartz.
   2018 [cited 2022 Dec 27]. Available from: https://qz.com/1198965/the-surprising-geography-of-opioid-use-around-the-world/
- Degenhardt L, Gisev N, Cama E, Nielsen S, Larance B, Bruno R. The extent and correlates of community-based pharmaceutical opioid utilisation in Australia. Pharmacoepidemiol Drug Saf. 2016;25(5):521–38.
- 5. Ambekar: Magnitude of substance use in India Google Scholar [Internet]. [cited 2022 Dec 27]. Available from: https://scholar.google.com/scholar\_lookup?title=Magnitude%20of%20Substance%20Us e%20in%20India&author=A%20Ambekar&author=A%20Agrawal&author=R%20Rao &publication\_year=2019&book=Magnitude%20of%20Substance%20Use%20in%20India
- 6. Singh B, Rao R. Is there an opioid epidemic in India? J Public Health. 2021 Oct;43(Supplement\_2):ii43-50.
- Ganguly KK, Sharma HK, Krishnamachari K a. VR. An ethnographic account of opium consumers of Rajasthan (India): socio-medical perspective. Addiction. 1995;90(1):9–12.
- 8. Trang T, Al-Hasani R, Salvemini D, Salter MW, Gutstein H, Cahill CM. Pain and Poppies: The Good, the Bad, and the Ugly of Opioid Analgesics. J Neurosci. 2015 Oct 14;35(41):13879–88.
- Younger JW, Chu LF, D'Arcy NT, Trott KE, Jastrzab LE, Mackey SC. Prescription opioid analgesics rapidly change the human brain. PAIN. 2011 Aug;152(8):1803.

- Hina N, Fletcher D, Poindessous-Jazat F, Martinez V. Hyperalgesia induced by low-dose opioid treatment before orthopaedic surgery: An observational case-control study. Eur J Anaesthesiol EJA. 2015 Apr;32(4):255.
- Pawan M, Choudhary R, Mathur R, Choudhary MR, Kamla M. Study On Harmful Effects Of Opium On Liver And Lungs In Chronic Opium Addicts Of Western Rajasthan. J Bangladesh Soc Physiol. 2011;6(2):122-6.
- Menendez ME, Ring D, Bateman BT. Preoperative Opioid Misuse is Associated With Increased Morbidity and Mortality After Elective Orthopaedic Surgery. Clin Orthop Relat Res. 2015 Jul;473(7):2402–12.
- Zywiel MG, Stroh DA, Lee SY, Bonutti PM, Mont MA. Chronic opioid use prior to total knee arthroplasty. J Bone Joint Surg Am. 2011 Nov 2;93(21):1988–93.
- 14. Pivec R, Issa K, Naziri Q, Kapadia BH, Bonutti PM, Mont MA. Opioid use prior to total hip arthroplasty leads to worse clinical outcomes. Int Orthop. 2014 Jun;38(6):1159–65.
- 15. Saeed Sadeghian MD, Abbasali Karimi MD, Samaneh Dowlatshahi MD, Seyed Hossein Ahmadi MD, Saeed Davoodi MD, Mehrab Marzban MD, et al. The association of opium dependence and postoperative complications following coronary artery bypass graft surgery: A propensity-matched study. J Opioid Manag. 2009;5(6):365–72.
- Safaii N, Kazemi B. Effect of opium use on short-term outcome in patients undergoing coronary artery bypass surgery. Gen Thorac Cardiovasc Surg. 2010 Feb 1;58(2):62-7.
- Cron DC, Englesbe MJ, Bolton CJ, Joseph MT, Carrier KL, Moser SE, et al. Preoperative Opioid Use is Independently Associated With Increased Costs and Worse Outcomes After Major Abdominal Surgery. Ann Surg. 2017 Apr;265(4):695–701.
- Waljee JF, Cron DC, Steiger RM, Zhong L, Englesbe MJ, Brummett CM. Effect of Preoperative Opioid Exposure on Healthcare Utilization and Expenditures Following Elective Abdominal Surgery. Ann Surg. 2017 Apr;265(4):715–21.
- Malviya A, Negi N, Mandora M, Yadav JK. Perioperative Status and Complications in Opium Addicts in Western Rajasthan. Indian J Surg. 2011 Oct 1;73(5):346–51.

- 20. Kosten TR, Haile CN. Opioid-Related Disorders. In: Loscalzo J, Fauci A, Kasper D, Hauser S, Longo D, Jameson JL, editors. Harrison's Principles of Internal Medicine [Internet]. 21st ed. New York, NY: McGraw-Hill Education; 2022 [cited 2022 Dec 27]. Available from: accessmedicine.mhmedical.com/content.aspx?aid=1190511475
- 21. View Large | AccessMedicine | McGraw Hill Medical [Internet]. [cited 2022 Dec 27].

  Available from:

  https://accessmedicine.mhmedical.com/ViewLarge.aspx?figid=266395194&gbosContai

  nerID=0&gbosid=0&groupID=0&sectionId=265468653&multimediaId=undefined
- 22. Yaksh T, Wallace M. Opioids, Analgesia, and Pain Management. In: Brunton LL, Hilal-Dandan R, Knollmann BC, editors. Goodman & Gilman's: The Pharmacological Basis of Therapeutics [Internet]. 13th ed. New York, NY: McGraw-Hill Education; 2017 [cited 2022 Dec 27]. Available from: accessmedicine.mhmedical.com/content.aspx?aid=1162536611
- 23. Porter J, Jick H. Addiction rare in patients treated with narcotics. N Engl J Med. 1980 Jan 10;302(2):123.
- Acute pain management: operative or medical procedures and trauma, Part 2. Agency for Health Care Policy and Research. Clin Pharm. 1992 May;11(5):391–414.
- 25. Magnitude\_Substance\_Use\_India\_REPORT.pdf [Internet]. [cited 2022 Dec 27]. Available from: https://www.muktangan.org/pdf/Magnitude\_Substance\_Use\_India\_REPORT.pdf
- 26. Team. Opium-Doda Addiction in Rajasthan: Social Issue [Internet]. RajRAS | RAS Exam Preparation. 2016 [cited 2022 Dec 27]. Available from: https://www.rajras.in/opium-doda-addiction-rajasthan-social-issue/
- 27. Qureshi AA, Acharya R, Sharma G, Sethia R, Shekhawat K, Kawatra A. An epidemiological study to assess prevalence and behavior related to substance abuse among urban Bikaner population Rajasthan. Int J Community Med Public Health. 2017 Aug 23;4(9):3338–41.
- 8. Administration SA and MHS. Substance Use Disorders [Internet]. Impact of the DSM-IV to DSM-5 Changes on the National Survey on Drug Use and Health [Internet].

- Substance Abuse and Mental Health Services Administration (US); 2016 [cited 2022 Dec 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519702/
- 29. Administration SA and MHS. Table 2.1, Comparison of DSM-IV, DSM-5, and NSDUH Substance Use Disorder Assessment [Internet]. Substance Abuse and Mental Health Services Administration (US); 2016 [cited 2022 Dec 28]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519702/table/ch2.t1/
- 30. Sabiston Textbook of Surgery 21st Edition [Internet]. [cited 2022 Dec 28]. Available from: https://www.elsevier.com/books/sabiston-textbook-of-surgery/townsend/978-0-323-64062-6
- 31. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo Classification of Surgical Complications: Five-Year Experience. Ann Surg. 2009 Aug;250(2):187–96.
- 32. McKay A, Sutherland FR, Bathe OF, Dixon E. Morbidity and mortality following multivisceral resections in complex hepatic and pancreatic surgery. J Gastrointest Surg Off J Soc Surg Aliment Tract. 2008 Jan;12(1):86–90.
- 33. Arru M, Pulitanò C, Aldrighetti L, Catena M, Finazzi R, Ferla G. A prospective evaluation of ultrasonic dissector plus harmonic scalpel in liver resection. Am Surg. 2007 Mar;73(3):256-60.
- 34. Mentula PJ, Leppäniemi AK. Applicability of the Clavien-Dindo classification to emergency surgical procedures: a retrospective cohort study on 444 consecutive patients. Patient Saf Surg. 2014 Dec;8(1):1-7.
- 35. Lee D, Armaghani S, Archer KR, Bible J, Shau D, Kay H, et al. Preoperative Opioid Use as a Predictor of Adverse Postoperative Self-Reported Outcomes in Patients Undergoing Spine Surgery. J Bone Joint Surg Am. 2014 Jun 4;96(11):e89.
- 36. Maeda A, Bateman BT, Clancy CR, Creanga AA, Leffert LR. Opioid abuse and dependence during pregnancy: temporal trends and obstetrical outcomes. Anesthesiology. 2014 Dec;121(6):1158-65.

- Oderda GM, Said Q, Evans RS, Stoddard GJ, Lloyd J, Jackson K, et al. Opioid-Related Adverse Drug Events in Surgical Hospitalizations: Impact on Costs and Length of Stay. Ann Pharmacother. 2007 Mar 1;41(3):400-7.
- 38. Azarasa M, Azarfarin R, Changizi A, Alizadehasl A. Substance use among Iranian cardiac surgery patients and its effects on short-term outcome. Anesth Analg. 2009 Nov;109(5):1553–9.
- Dewan KC, Dewan KS, Idrees JJ, Navale SM, Rosinski BF, Svensson LG, et al. Trends and Outcomes of Cardiovascular Surgery in Patients With Opioid Use Disorders. JAMA Surg. 2019 Mar 1;154(3):232–40.
- 40. Smith ME, Lee JS, Bonham A, Varban OA, Finks JF, Carlin AM, et al. Effect of new persistent opioid use on physiologic and psychologic outcomes following bariatric surgery. Surg Endosc. 2019 Aug 1;33(8):2649–56.
- 41. Mathur ML, Mahapatra A. A Reterospective Study of Opium Addicts in Deaddiction Camps and Rural Community in Western Rajasthan. J Hum Ecol. 1993 Oct 1;4(4):267–71.



# ANNEXURES



#### **ANNEXURES**

#### **ANNEXURE I**

#### Ethical clearance certificate



#### अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर All India Institute of Medical Sciences, Jodhpur संस्थागत नैतिकता समिति Institutional Ethics Committee

No. AIIMS/IEC/2021/ 2527

Date: 12/03/2021

#### ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: AIIMS/IEC/2021/3362

Project title: "Association between opium use disorder and postoperative complications in patients undergoing surgery in general surgery department of a tertiary care centre: A prospective cohort study"

Nature of Project:

Research Project Submitted for Expedited Review

Submitted as: Student Name: M.S. Dissertation Dr. M.V.R. Abhishek Dr. Mahendra Lodha

Guide:

Dr. Ashok Puranik & Dr. Navratan Suthar

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- · Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- · Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IFC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Frayed Sharma Member Secretary Member Secretary Institutional Ethics Convolute AllBas, Josephyson

Basni Phase-2, Jodhpur, Rajasthan-342005; Website: www.aiimsjodhpur.edu.in; Phone: 0291-2740741 Extn. 3109
E-mail: ethicscommittee@aiimsjodhpur.edu.in; ethicscommitteeaiimsjdh@gmail.com

#### **ANNEXURE II**

#### **INFORMED CONSENT FORM (English)**

Title of Thesis/Dissertation:

"ASSOCIATION BETWEEN OPIUM USE DISORDER AND POSTOPERATIVE COMPLICATIONS IN PATIENTS UNDERGOING SURGERY IN GENERAL SURGERY DEPARTMENT OF A TERTIARY CARE CENTRE: A PROSPECTIVE COHORT STUDY"

Name of PG Student : Dr ABHI	SHEK MANTHRI (Mobile No.:9959147879)					
	No. :					
	S/o or D/o					
	give my full, free, voluntary consent to be a part of					
the study "ASSOCIATION	BETWEEN OPIUM USE DISORDER AND					
POSTOPERATIVE COMPLIC	CATIONS IN PATIENTS UNDERGOING SURGERY					
IN GENERAL SURGERY DE	EPARTMENT OF A TERTIARY CARE CENTRE: A					
PROSPECTIVE COHORT ST	UDY", procedure and nature of which has been explained to					
me in my own language to my fu	ull satisfaction. I confirm that I have had the opportunity to					
ask questions.						
I understand that my participation	n is voluntary and I am aware of my right to opt out of the					
study at any time without giving a	iny reason.					
I understand that the information	collected about me and any of my medical records can be					
seen by the person responsible for	the regulatory authorities.					
Date:						
Place:	Signature/Left thumb impression					
This to prove that the above conse	ent has been received in my presence.					
Date:						
Place:						
ignature of PG Student						
1. Witness 1	2. Witness 2					
Signature						
Name:	Name:					
Address:	Address:					

#### **ANNEXURE IV**

#### **PATIENT INFORMATION SHEET**

Title- ASSOCIATION BETWEEN OPIUM USE DISORDER AND POSTOPERATIVE COMPLICATIONS IN PATIENTS UNDERGOING SURGERY IN GENERAL SURGERY DEPARTMENT OF A TERTIARY CARE CENTRE: A PROSPECTIVE COHORT STUDY

Name:	Age/Gender:
Phone No:	

Address:

#### **AUTHORIZATION:**

I feel free to accept or refuse to participate in this study.

I have been informed that this study will be done to identify the prevalence of opioid use disorder by means of interview-based questionnaire. I am clearly informed that my identification will not be revealed in the result. I have understood that all my health information is accessible to the interviewer and the researcher. I have had a choice to ask questions and all my questions were answered to my satisfaction

I have been assured that the information obtained from me will solely be used for the purpose of the study and shall remain confidential.

By signing this form, I give my free and informed consent to take part in this study as outlined in the information sheet and this consent form. I understand that I am free to withdraw from the study at any given time. By signing up this form I have not given up my legal rights.

Hence, I hereby give my wilful consent for my inclusion in this study which is being conducted by the Department of General Surgery, All India Institute of Medical Sciences, Jodhpur by Dr Abhishek Manthri.

In any case of queries, you may contact:

Dr Abhishek Manthri

Academic Junior Resident, General Surgery

All India Institute of Medical Sciences, Jodhpur

Phone no. 9959147879

#### ANNEXURE V

### रोगी की सूचना पत्र

शीर्षकः ओप्पयम उपभोग बीमारी का और ऑपरेशन के बाद जटिलताओं की संबंध I

नामः

आयु / प्लंगः

फ़ोन नंबरः

पताः

प्राधिकारः

मैं इस अध्ययन में भाग अपनी मर्जी मुताबिक ले रहा हूं।

मुझे समझाया गया है क्र इस अध्ययन में दूरबीन जैसे उपकरणों का उपयोग होगा।अध्ययन के क्रिए दो समूह बनाए गए हैं जिसमें सर्जरी के क्रिए मुझे क्रिसी दो में से एक समूह में रखा जाएगा। दोनों समूह उपकरणों के माप को ध्यान में रखते हुए बनाए गए हैं। दोनों समूह के परिणामों के बारे में मुझे अच्छे से समझा दिया गया है। अध्ययन का उद्देश्य दोनों समूहों में हुए ऑपरेशन के बाद के दर्द की तुलना करना है। अध्ययन में मुझे 30 दिन तक रखा जाएगा, जिसमें दिन 7 और दिन 30 पर मुझे ऑपरेशन संबंधित मुझसे जुड़ी जानकारी देने के क्रिए बुलाया जाएगा।

मुझे अध्ययन और सर्जरी से संबंधित प्रश्न पूछने का पूरा मौका दिया गया जिनसे । मले जवाब से

मुझे पूरी संतुष्टि है।

मुझे पूरा आश्वासन दिलाया गया है की मुझसे ामली जानकारी को केवल और केवल अध्ययन के ातर इस्तेमाल क्रिया जाएगा, और मुझसे ामली जानकारी को पूरे तरीके से गोपनीय रखा जाएगा। मुझे यह समझाया गया है और मैं जानता हूं की मैं इस अध्ययन को अपनी इच्छा मुताबिक कभी भी

ष्रोड़ सकता हूं। सप्तर, मैं इस अध्ययन के प्लर अपनी इच्छा-सहमति प्रदान करता हूं, जो क्र जनरल सर्जरी प्रभाग, गल इंक्रया इंस्टिट्यूट ऑफ़ मेक्षकल साइंसेज, जोधपुर द्वारा डॉ. धीरेन कुमार गुप्ता द्वारा की जा

ही है। गनकारी संबंध्यत फ़ासी भी सवाल के प्लए संपर्क करें:

णिषेक मंत्री.

कादामक जूनियर रेजिडेंट, जनरल सर्जरी

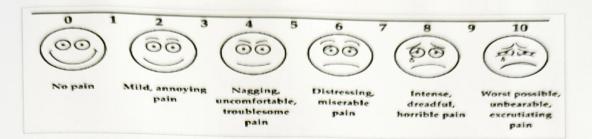
ाल इंडिया इंस्टिट्यूट ऑफ़ मेडिकल साइंसेज, जोधपुर

### ANNEXURE VI

### PATIENT PROFORMA

Demo	graphic details-		
Name	÷		
Age:		Sex:	
Relig	ion:		
Rural		Urban:	
Conta	ct number:		
Educa	tion status:		
Heigh	t (cm):	Weight (kg):	
Patien			
DOA-	//_ DOS//_		
	orbidities:		
A) Di	M B) HTN C) TB D) COPD	E) ASTHMA F) A	LLERGY G) OBESE
H)CA	NCER		
I) PVI	)		
DIAG	NOSIS-		
1.	Age of initiation of opium intake:		
2.	Form of opium intake:		
a. Afe	em/Amal b. Doda	c. Heroin	d. Opioid medication.
3.	Frequency of use:		
a.Dail	b. Weekly	c. Occasional	
4.	Other substance use:		
a. Alco	b. Tobacco	c. Ganja	d. LSD
5,	Method of initiation:		
a.Own	interest b. social customs	c. Pain relief.	
5.	Opioid use disorder present?		
. Yes	b. No		
7.	URGENCY OF SURGERY PERFO	ORMED:	
1.	Emergency b. Elective		
3.	Surgery performed:		
1,		paroscopic GI surgeries	d. Amputations
Oth.			

#### 9. VAS score at 12 hours:



- 10. Analgesia given:
- a. PCM
- b. PCM + TRAMADOL
- c. PCM + TRAMADOL + NSAIDS
- d. PCM + TRAMADOL + NSAIDS + OPIOIDS.
- e. Others (Epidural / regional blocks)
- 11. Clavien Dindo grade of post operative complications:
- 12. Post-operative day of initiation of bowel sounds: DAY:
- 13. Length of post-operative stay: DAY:

# ANNEXURE VII KEY TO MASTER CHART

CODE	DIAGNOSIS	
	VASCULAR ISCHEMIA/ THRMOBOSIS	
2	PERFORATION PERITONITIS	
3	TRAUMA	
4	INFECTION	
5	OBSTRUCTION	
6	HERNIA	
7	NEOPLASM	
8	APPENDICULAR DISEASES	
9	HEPATOBILIARY DISORDERS	
10	ANAL AND RECTAL DISORDERS	
ABBREVIATIONS		
VAS	VISUAL ANALOGUE SCALE	
TB	TUBERCULOSIS	
COPD	Chronic Obstructive Pulmonary Disease	
PVD	Peripheral Vascular Disease	
PCM	Paracetamol	
NSAIDS	Non steroidal anti inflammatory drugs	
SSI	Surgical Site Infection	

# ANNEXURE VIII MASTER CHART