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Effect of Intranasal Dexmedetomidine on Opioid - Sparing Effect in Patients Undergoing Abdominal Surgeries - A Pilot Study

Short Running Title: Opioid sparing effect of intranasal dexmedetomidine.

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Abstract: ***Background: The aim of this open - label, observational, pilot study was to determine the opioid - sparing effect in patients undergoing abdominal surgeries aged between 18 - 65 years. Methods: 50 patients were enrolled in this study as per inclusion criteria and were divided into two groups of 25 subjects. Group D had intranasal administration of dexmedetomidine and Group N was given a placebo. Patient's vitals, mRASS, and NRS were recorded pre - induction to medication, intraoperatively as well as postoperatively. Result: 50 patients were studied for intranasal dexmedetomidine in the Department of Anaesthesia and Critical Care, Bhopal Memorial Hospital and Research Centre, Bhopal. Based on the data analysis following observations were made. Patients of both groups were comparable concerning age, BMI, gender, and ASA grading. These two groups are compared based on mean arterial pressure (MAP), respiratory rate (RR), heart rate (HR), numerical rating scale (NRS), modified Richmond agitation sedation score (mRASS) and oxygen saturation (SpO_2). Conclusion: The findings in this study suggested that intranasal dexmedetomidine had a significant effect on Heart Rate, Mean Arterial Pressure, less effect on Respiratory Rate, and Oxygen Saturation, providing an opioid - sparing effect by reducing postoperative pain.***

Keywords: abdominal surgeries, dexmedetomidine, intranasal, opioid – sparing

1. Introduction

Patients who undergo surgeries are often exposed to opioids during and after the procedure, which can result in postoperative pain, hemodynamic instability, agitation, and behavioural changes. Therefore, as an anaesthesiologist, it is crucial to manage the dosage of opioids and help patients deal with postoperative stress and agitation.

Dexmedetomidine is an alpha - 2 adrenoceptor agonist having effect of sedation, anxiolysis, sympatholytic, and analgesia - sparing effects. It is highly potent having minimal respiratory depression and high selectivity for alpha 2: alpha1 – 1620: 1. Its hypnotic effect comes after activation of pre and post - synaptic alpha 2 receptors in locus coeruleus, an important nucleus mediating sympathetic nervous system function, vigilance, memory, analgesia, and arousal. The sedative effects produced by dexmedetomidine are mainly due to the inhibition of this nucleus. It induces unconsciousness like normal sleep so that the patient remains arousable and cooperative.

Compared with traditional analgo - sedative agents like opioids, dexmedetomidine has less effect on respiration. The quality of sedation produced by alpha 2 agonists differs from sedation produced by drugs that act on GABA receptors Drugs that activate GABA receptors can cloud consciousness, cause agitation paradoxically, and lead to tolerance and dependence. Improving the quality of postoperative care can lead to higher satisfaction among patients who have undergone surgery.

Intranasal administration is a method that offers several benefits. This route of administration does not require intravenous access to achieve anxiolysis, making it a comfortable and well - tolerated method of sedation. Administering dexmedetomidine intranasally can be a safe and effective route for sedation. This method is less invasive, well - tolerated by individuals, and has a rapid onset of action due to the high vascularity of nasal mucosa.

The purpose of this study was to investigate whether intranasal dexmedetomidine could reduce opioid

consumption during and after surgery. Additionally, we examined whether intranasal dexmedetomidine could decrease postoperative restlessness, agitation, and pain.

The pharmacological effect of intravenous dexmedetomidine has been extensively studied for perioperative use and has been shown to improve patients' first night sleep after surgery, particularly in the paediatric population. Our pilot study was designed to investigate the effects of intranasal dexmedetomidine in adult patients.

1.1 Aim

This study aims to report preliminary data on the use of intranasal dexmedetomidine on opioid - sparing effects in patients undergoing abdominal surgeries.

1.2 Objectives

Primary Objective –
- To study opioid - sparing effect on intranasal dexmedetomidine.

Secondary Objective –
- To study the effect of dexmedetomidine on postoperative restlessness, agitation and pain.
- To study effect on hemodynamic responses of intranasal dexmedetomidine in the postoperative period.

2. Material and Methods

Source of Data
This study was conducted in Department of Anaesthesia and Critical Care, Bhopal Memorial Hospital and Research Centre, Bhopal.50 consecutive patients who underwent abdominal surgery under general anaesthesia from August 2022 to May 2023 were enrolled for the study.

Type of study: prospective open - label observational study.

Name of Institute: Department of Anaesthesiology and Critical Care, BMHRC, Bhopal.

Conflict of interest: None

Ethical clearance: Ethical clearance was taken from institutional ethical committee BMHRC Bhopal.

Study population: All adult patients presenting for abdominal surgery in anaesthesia department at BMHRC during study period.

Sample Size: This study will be a pilot study to see the effect of intranasal dexmedetomidine for opioid sparing effect in patient undergoing surgery. The sample size will include restricted number of patients. Each group will include 25 patients.

Inclusion Criteria - All ASA grade I, II of age 18 - 65 years undergoing abdominal surgery under general anaesthesia.

Exclusion Criteria -
Patient who did not give consent for study.
Patient with second degree atrioventricular block, third degree atrioventricular block.
Patient on antiarrhythmic drugs.
Patient on psychiatric illness/ treatment.
Duration of surgery > 3 hours.
With known hypersensitivity to the drug.
Patients on cardiovascular treatment including antihypertensive medication.
Patients having neurological comorbidity
Alcohol abuser
History of nasal surgery

All patients for abdominal surgeries meeting inclusion criteria were included in the study following written and informed consent. An 18 - gauge intravenous cannula was inserted in the forearm and the lactated ringer's solution was infused at 8 ml/kg/hour. Patient's vitals, Modified Richmond Agitation Score (mRASS) and numerical rating scale (NRS) were recorded pre - induction to the medication and taken as baseline vitals.

Patients were randomly divided by using the calendar method into two groups: **D group** patients received intranasal dexmedetomidine 30 minutes before induction in the pre - operative area with a dose of 1 µg/kg, the maximum dose was 100 µg which was approximately 1.6 ml and this was introduced in each nostril by drop method. **N group** of patients received intranasal normal saline 0.9% of 1 ml with the same method in each nostril.

A registered nurse in the preoperative room gave medication to the patients according to randomization given by the investigator. For induction in both groups, the induction agent used was propofol 1.5 – 2 mg/kg, fentanyl 1 - 2 µg /kg, neuromuscular blocker (rocuronium 1 mg/kg or vecuronium 0.1 mg/kg), and injection paracetamol 1 gm was given. During surgery, vitals including heart rate, non - invasive blood pressure, and oxygen saturation (SpO2) were taken at regular intervals (every 5 minutes up to 30 minutes) and then hourly. After completion of surgery, postoperative vitals were noted along with m RASS (Modified Richmond Agitation and Sedation Score) and NRS (numerical rating scale) at regular intervals till 6 hours after completion of surgery

Intranasal dexmedetomidine was administered using a syringe via the drop method by a registered nurse in the recovery room. The patients were kept in the supine position and the drug was administered in both nostrils after which the nose was pinched for 30 seconds.

The assessment included observation of baseline vitals - Heart Rate, Blood Pressure, Respiratory Rate, SpO2 and intraoperatively Heart Rate, Blood Pressure, Respiratory Rate, and SpO_2 at regular intervals from 5 minutes, 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours. Total opioid used during surgery was also recorded. In the postoperative period – Heart Rate, Blood Pressure, Respiratory Rate, sPO_2, mRASS scoring, and NRS scoring were observed at regular intervals starting from 5 minutes, 10 minutes, 15 minutes, and 30 minutes then 1 hour, 2 hours, 4 hours, and 6 hours.

Any adverse events like ECG changes, hypotension, loss of consciousness, need for vasopressor infusion, assisted

ventilation, or intubation, and the requirement for postoperative analgesia were also recorded for the study.

Statistical Analysis:
This single - centre, open - label, pilot study was conducted among 50 patients aged 18 - 65 years undergoing laparoscopic abdominal surgery from August 2022 to July 2023 at Bhopal Memorial Hospital and Research Centre, Bhopal, Madhya Pradesh and data analysis was performed between July to September 2023. The data was entered into an Excel sheet and analyzed using SPSS software. The results are presented as the mean value with the standard deviation (SD). Categorical data was compared using chi - square analysis, and for continuous data, *t* - test analysis was used. All data was analysed by using the Statistical Package of Social Sciences (SPSS Software Version 21) and a two - way RMANOVA tool was used. If *P value* < 0.05, then result will be considered significant.

3. Results

50 patients were studied for intranasal dexmedetomidine in the Department of Anaesthesia and Critical Care, Bhopal Memorial Hospital and Research Centre, Bhopal. Based on the data analysis following observations were made. Patients of both groups were comparable concerning age, BMI, gender, and ASA grading. These two groups are compared based on mean arterial pressure (MAP), respiratory rate (RR), heart rate (HR), numerical rating scale (NRS), modified Richmond agitation sedation score (mRASS) and oxygen saturation (SpO_2).

In group D, patients had heart rates between 60 - 80 /min intraoperatively as well as postoperatively. One case had a heart rate drop of up to 48 beats per minute and was treated with an injection of atropine 0.6 mg intravenously and thus the case was completed. In group N, patients had heart rates in a high physiological range between 80 – 100 intraoperatively and postoperatively. In the postoperative period, the heart rate settled after pain relief (table II).

In both groups, patients had mean arterial pressure (MAP) within the normal range of 65 to 100 mmHg intraoperatively and postoperatively as well. In group N patients had a higher range of MAP intraoperatively as well as postoperatively. Both the groups showed that systolic blood pressure is in the normal range of 100 - 140 mmHg but in group N patient's systolic BP was in the higher range of physiological values both in the intraoperative and postoperative period. Group D had diastolic blood pressure within the physiological range whereas Group N patients had diastolic blood pressure in the higher range (table I).

mRASS scale is assessed in the postoperative period after extubation. Using the two - way RMANOVA tool with a mean of 0.9 and SD of 0.6±0.3 (P - value<0.001), indicated that Group D patients had higher baseline values in the postoperative period than Group N patients (table III).

Group D patients' total usage of opioids was significantly less as compared to Group N patients intraoperatively. Using the two - way RMANOVA tool, the mean was 114.8 with SD 24.5 (P - value<0.001) implying that in group D patients, the opioid dosage was not repeated other than the induction dose.

In the postoperative period, 92% of patients of Group D received rescue analgesia after 6 hours whereas 76% of patients of Group N patients received rescue analgesia within 6 hours.

NRS is assessed in the postoperative period. In both these groups, pain in the postoperative period was managed using an injection of paracetamol and injection of diclofenac. Group D patients showed lower values on NRS that got settled within a few minutes on their own without giving any rescue analgesia. In this group, two patients had NRS values of 8 and 6 that were managed with an injection of diclofenac 75 mg, and an injection of paracetamol within 1 hour (a patient who had an NRS scale of 8 was given an injection of tramadol 50 mg within the first hour of the postoperative period). Injection of paracetamol was repeated after 6 hours in all other patients. For Group N patients, NRS values were in the range of 2 - 5 and persisted for 1 – 2 hours. The patient was administered an injection of diclofenac within 1 hour and an injection of paracetamol within 6 hours (table IV).

Intraoperatively, group D had a respiratory rate within the physiological range, while group N had a respiratory rate on the higher side. The same was observed in the immediate postoperative period. In the late postoperative period, patients in both groups had respiratory rates within the physiological range. Thus, it shows that intranasal dexmedetomidine had little effect on the respiratory system. The graph shows that in both groups' saturation was maintained at more than 95 %. So, this parameter was relatively unaffected (table V).

1)

Two way RMANOVA				p-values	
Group D		Group N		Within time interval	Between groups
Mean	SD	Mean	SD		
79.6	8.8	80.7	16.1	0.001	0.201
79.5	8.3	84.1	16		
81.4	10.1	87.5	15.9		
81.8	7.2	87.9	16.1		
84.2	10.3	86.9	15.3		
29.4	40.3	50	45.3		

2)

Two way RMANOVA				p-values	
Group D		Group N		Within time interval	Between groups
Mean	SD	Mean	SD		
79.7	12.6	82.6	12.6	<0.001	<0.001
75.2	12.6	91.9	3.9		
73.3	11.9	90.7	3.7		
70.8	11.5	89.6	3.7		
68.5	10.7	88.2	3.4		
67.8	10.5	85.7	4.2		
69.5	9	81.1	15.8		
70.6	8.4	82.3	5		
70.6	9.1	79.3	6.2		

3)

Two way RMANOVA				p-values	
Group D		Group N		Within time interval	Between groups
Mean	SD	Mean	SD		
0	0	0	0	<0.001	<0.001
0.9	0.9	3	1.2		
0.6	0.8	2.9	1		
0.3	0.5	2.5	1		
0	0.2	2.3	0.8		
0	0	1.4	1.1		
0	0	1	1.2		
0	0	0.4	0.8		
0	0	0	0		

4)

Two way RMANOVA				p-values	
Group D		Group N		Within time interval	Between groups
Mean	SD	Mean	SD		
1.6	2	1.6	0.7	<0.001	<0.001
0.1	0.4	0	0		
1.6	2	1.5	0.5		
1.6	2	1.2	0.5		
0.9	1.6	0.9	0.6		
0.4	1	0.4	0.6		
0.3	0.7	0.2	0.4		
0	0	0	0		
0	0	0	0		

5)

Two way RMANOVA				p-values	
Group D		Group N		Within time interval	Between groups
Mean	SD	Mean	SD		
98.9	1.2	99.9	0.3	<0.001	<0.001
99.8	0.5	100	0		
100	0	100	0		
100	0	100	0		
100	0	100	0		
100	0	100	0		
36	49	56	50.7		
99.8	0.7	100	0		
99.8	0.7	100	0		
99.7	0.7	100	0		
99.7	0.7	100	0		
99.5	0.8	100	0		
99.2	0.9	99.9	0.3		
99	1	99.7	0.5		
99.1	1	99.9	0.3		

1) Comparison of both the groups for MAP (mean arterial pressure)
2) Comparison of both the groups for HR showing p-value<0.001
3) Comparison for both the groups for mRASS showing p-value<0.001
4) Comparison for both the groups for NRS showing p-value <0.001
5) Comparison for both the groups for SpO_2 showed no significant difference

4. Discussion

Dexmedetomidine has antiemetic and analgesic effects compared with other premedications. The intranasal route is highly effective as hepatic first - pass metabolism can be bypassed. The systemic bioavailability is therefore high and there is rapid absorption. Intranasal administration is often preferred due to its ease of administration and bolus dosing compared to intravenous administration. It causes conscious drowsiness, meaning that patients can be woken up by a gentle tap or vocal command.

The weight - adjusted mean dexmedetomidine dose used in this study was 1 mcg/kg, which is lower than the doses used in other studies. One study used 1 - 2 mcg/kg in geriatric patients[5], while another study used 1 - 2 mcg/kg for intranasal dexmedetomidine premedication in children[16, 17]. One study used a dose of 2 mcg/kg in paediatric patients in his study[12]. Administration of intranasal dexmedetomidine had a lowering effect on heart rate, MAP and systolic blood pressure. In some studies, it is concluded in his study that there is a decrease in heart rate, and mean arterial pressure but no change in respiratory rate and oxygen saturation[5, 7].

Respiratory rate and oxygen saturation remain unaffected in the patient intraoperatively as well as postoperatively after administration of intranasal dexmedetomidine. Recent studies have shown that sedation with dexmedetomidine decreases hypoxic ventilatory response similar to propofol in healthy volunteers[10, 11]. Thus respiratory monitoring is required. In our study, intranasal dexmedetomidine administration led to a decrease in heart rate, mean arterial pressure, and systolic blood pressure within the physiological range with no effect on respiratory rate and saturation intraoperatively as well as in the postoperative period.

Opioids have traditionally been the cornerstone of postoperative analgesia and there is an increasing concern about opioid - induced adverse effects worldwide as can be seen in studies[6]. Opioids are associated with an increased risk of postoperative delirium seen in the studies[18] and postoperative pain also had negative effects on mental status and anxiety that should be treated promptly. Some study also supports the analgesic effect of intranasal dexmedetomidine and also that it reduces opioid consumption and helps in reducing postoperative pain. Another study also supports that intranasal dexmedetomidine could deliver more effective postoperative analgesia[12]. This pilot study made it evident that there was no repetition of opioids other than dose during intubation in group D patients intraoperatively. Secondly, lower scores of NRS with first rescue analgesia used after 6 hours of postoperative observation showed that intranasal dexmedetomidine administration helped in the reduction of postoperative pain. So, the use of dexmedetomidine helps in the reduction of opioid consumption.

Treatment of postoperative restlessness and agitation can be challenging for healthcare professionals. One study showed that even a small dose of intranasal dexmedetomidine in geriatric patients was sufficient in reducing postoperative restlessness and agitation[5]. In contrast, another study showed that premedication with intranasal dexmedetomidine prevents postoperative emergency agitation in paediatric patients[14].

Some studies also support that the administration of intranasal dexmedetomidine reduces the emergence of delirium in children in post - anaesthesia care units[15]. In our study, postoperative agitation which was measured using the mRASS scale showed values within normal limits,

implicating that administration of intranasal dexmedetomidine helps in reducing postoperative restlessness and agitation. The use of dexmedetomidine as a part of multimodal analgesia can be beneficial in patients undergoing surgery. It can be used as an adjuvant to other agents. It has been shown to reduce the dose of opioids, and benzodiazepines which are deliriogenic.

Additionally, it is worth mentioning that an adverse event was observed in one patient who received intravenous atropine 0.6 mg for an episode of bradycardia (<40 beats per minute). Furthermore, there were no serious adverse events observed during the study. Intranasal dexmedetomidine is well tolerated by adult patients as well.

Nasal irritation was not observed or reported by any of the patients. In Group D patients, mRASS values were maintained at baseline values as compared to Group N patients and it was statistically significant. Similarly, pain severity measurements using NRS were significantly lower in Group N, 8% in Group D patients and 76% in Group D patients. Group D patients showed more hemodynamic stability as compared to Group N patients intraoperatively as well as in the postoperative period. Oxygen saturation was maintained above 95% in both groups. Respiratory rate was within the physiological range in both groups. Group N patients had higher respiratory rates, but not statistically significant.

5. Conclusion

The findings in this study suggest that intranasal dexmedetomidine has a significant effect on heart rate, mean arterial pressure, less effect on respiratory rate and oxygen saturation, giving opioid - sparing effect by reducing postoperative pain and can be a possible option for treatment of postoperative agitation and restlessness. The optimal dose and proper drug delivery system for intranasal dexmedetomidine dosing still remains to be evaluated.

6. Limitation

The optimal dose and proper drug delivery system for intranasal dexmedetomidine dosing remains to be evaluated. One potential limitation of this study is that with intranasal administration, a portion of the drug may reach the pharynx and be swallowed, which could alter the drug absorption rate.

7. Recommendation

We recommend more studies to be done for the evaluation of proper drug delivery systems for intranasal dexmedetomidine in adult patients.

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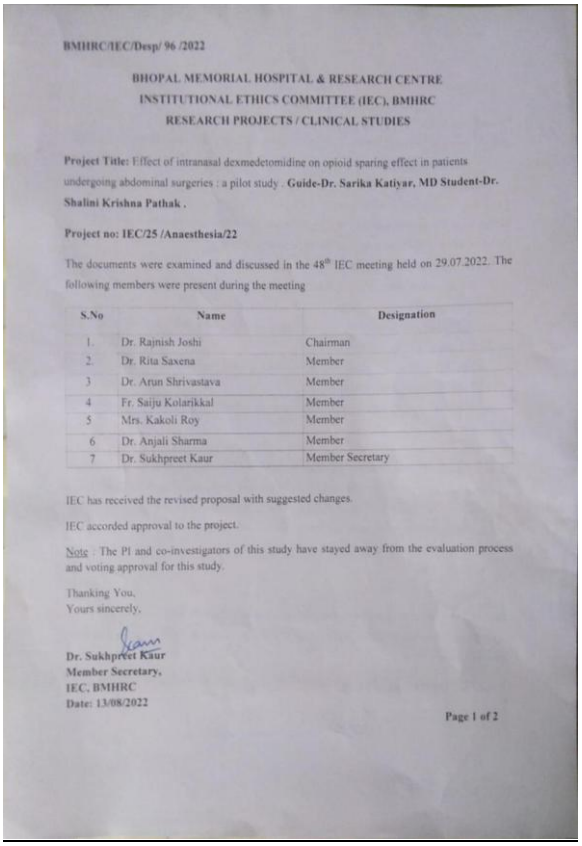
IEC CERTIFICATE -



BMHRC/IEC/Desp/ 96 /2022

BHOPAL MEMORIAL HOSPITAL & RESEARCH CENTRE
INSTITUTIONAL ETHICS COMMITTEE (IEC), BMHRC
RESEARCH PROJECTS / CLINICAL STUDIES

Project Title: Effect of intranasal dexmedetomidine on opioid sparing effect in patients undergoing abdominal surgeries : a pilot study . **Guide-Dr. Sarika Katiyar, MD Student-Dr. Shalini Krishna Pathak .**

Project no: IEC/25 /Anaesthesia/22

The documents were examined and discussed in the 48th IEC meeting held on 29.07.2022. The following members were present during the meeting

S.No	Name	Designation
1.	Dr. Rajnish Joshi	Chairman
2.	Dr. Rita Saxena	Member
3	Dr. Arun Shrivastava	Member
4	Fr. Saiju Kolarikkal	Member
5	Mrs. Kakoli Roy	Member
6	Dr. Anjali Sharma	Member
7	Dr. Sukhpreet Kaur	Member Secretary

IEC has received the revised proposal with suggested changes.

IEC accorded approval to the project.

Note : The PI and co-investigators of this study have stayed away from the evaluation process and voting approval for this study.

Thanking You,
Yours sincerely,

Dr. Sukhpreet Kaur
Member Secretary,
IEC, BMHRC
Date: 13/08/2022

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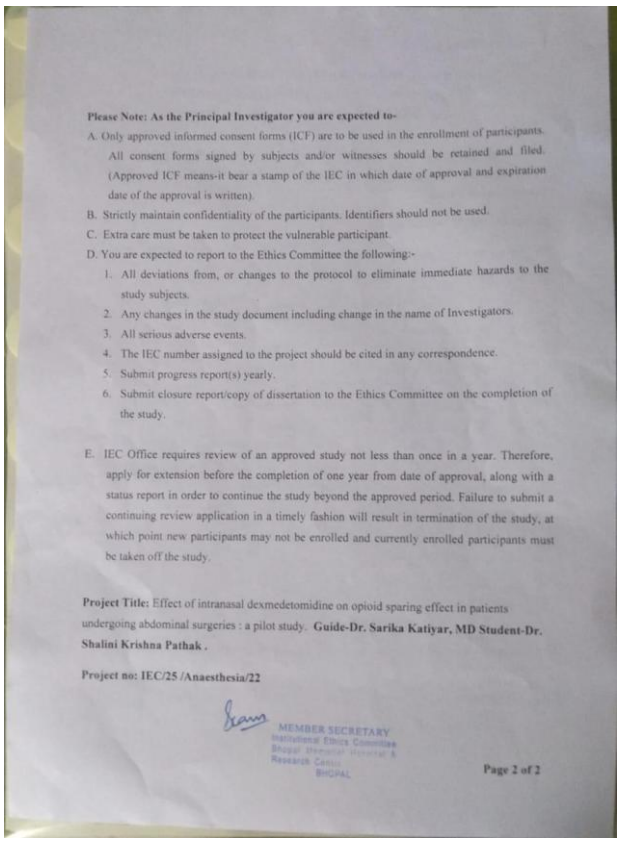

Please Note: As the Principal Investigator you are expected to-

A. Only approved informed consent forms (ICF) are to be used in the enrollment of participants. All consent forms signed by subjects and/or witnesses should be retained and filed. (Approved ICF means-it bear a stamp of the IEC in which date of approval and expiration date of the approval is written).
B. Strictly maintain confidentiality of the participants. Identifiers should not be used.
C. Extra care must be taken to protect the vulnerable participant.
D. You are expected to report to the Ethics Committee the following:-
1. All deviations from, or changes to the protocol to eliminate immediate hazards to the study subjects.
2. Any changes in the study document including change in the name of Investigators.
3. All serious adverse events.
4. The IEC number assigned to the project should be cited in any correspondence.
5. Submit progress report(s) yearly.
6. Submit closure report/copy of dissertation to the Ethics Committee on the completion of the study.

E. IEC Office requires review of an approved study not less than once in a year. Therefore, apply for extension before the completion of one year from date of approval, along with a status report in order to continue the study beyond the approved period. Failure to submit a continuing review application in a timely fashion will result in termination of the study, at which point new participants may not be enrolled and currently enrolled participants must be taken off the study.

Project Title: Effect of intranasal dexmedetomidine on opioid sparing effect in patients undergoing abdominal surgeries : a pilot study. **Guide-Dr. Sarika Katiyar, MD Student-Dr. Shalini Krishna Pathak .**

Project no: IEC/25 /Anaesthesia/22

MEMBER SECRETARY
Institutional Ethics Committee
Bhopal Memorial Hospital & Research Centre
BHOPAL

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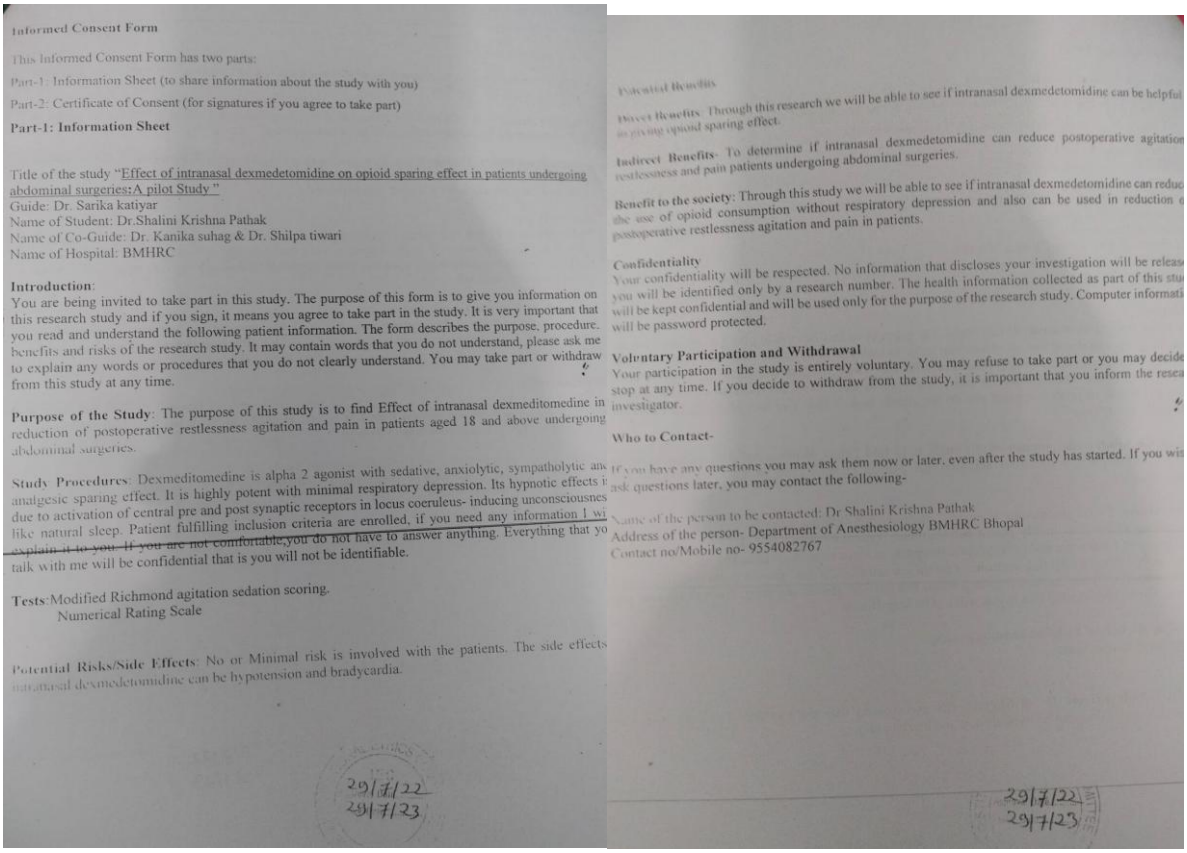
Consent Form -



Informed Consent Form

This Informed Consent Form has two parts:

Part-1: Information Sheet (to share information about the study with you)

Part-2: Certificate of Consent (for signatures if you agree to take part)

Part-1: Information Sheet

Title of the study "Effect of intranasal dexmedetomidine on opioid sparing effect in patients undergoing abdominal surgeries:A pilot Study "
Guide: Dr. Sarika katiyar
Name of Student: Dr.Shalini Krishna Pathak
Name of Co-Guide: Dr. Kanika suhag & Dr. Shilpa tiwari
Name of Hospital: BMHRC

Introduction:
You are being invited to take part in this study. The purpose of this form is to give you information on this research study and if you sign, it means you agree to take part in the study. It is very important that you read and understand the following patient information. The form describes the purpose, procedure, benefits and risks of the research study. It may contain words that you do not understand, please ask me to explain any words or procedures that you do not clearly understand. You may take part or withdraw from this study at any time.

Purpose of the Study: The purpose of this study is to find Effect of intranasal dexmeditomedine in reduction of postoperative restlessness agitation and pain in patients aged 18 and above undergoing abdominal surgeries.

Study Procedures: Dexmeditomedine is alpha 2 agonist with sedative, anxiolytic, sympatholytic and analgesic sparing effect. It is highly potent with minimal respiratory depression. Its hypnotic effects is due to activation of central pre and post synaptic receptors in locus coeruleus- inducing unconsciousnes like natural sleep. Patient fulfilling inclusion criteria are enrolled, if you need any information I wi explain it to you. If you are not comfortable,you do not have to answer anything. Everything that yo talk with me will be confidential that is you will not be identifiable.

Tests:Modified Richmond agitation sedation scoring.
Numerical Rating Scale

Potential Risks/Side Effects: No or Minimal risk is involved with the patients. The side effects intranasal dexmedetomidine can be hypotension and bradycardia.

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Potential Benefits

Direct Benefits: Through this research we will be able to see if intranasal dexmedetomidine can be helpful in giving opioid sparing effect.

Indirect Benefits- To determine if intranasal dexmedetomidine can reduce postoperative agitation restlessness and pain patients undergoing abdominal surgeries.

Benefit to the society: Through this study we will be able to see if intranasal dexmedetomidine can reduc the use of opioid consumption without respiratory depression and also can be used in reduction o postoperative restlessness agitation and pain in patients.

Confidentiality
Your confidentiality will be respected. No information that discloses your investigation will be releas you will be identified only by a research number. The health information collected as part of this stu will be kept confidential and will be used only for the purpose of the research study. Computer informati will be password protected.

Voluntary Participation and Withdrawal
Your participation in the study is entirely voluntary. You may refuse to take part or you may decide stop at any time. If you decide to withdraw from the study, it is important that you inform the resea investigator.

Who to Contact-

If you have any questions you may ask them now or later, even after the study has started. If you wis ask questions later, you may contact the following-

Name of the person to be contacted: Dr Shalini Krishna Pathak
Address of the person- Department of Anesthesiology BMHRC Bhopal
Contact no/Mobile no- 9554082767

29/7/22
29/7/23

GRAPHS:

Graph D.docx Graph C.docx Graph B.docx Graph A.docx