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Original Research Article

# Analgesic Effect of Intrathecal Morphine for Postoperative Analgesia in Cytoreductive Surgery in Comparison with Placebo Control: A Randomnised Controlled Trial

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**Conflict of interest: Nil**

**Abstract**

A hospital based open label observational study was conducted in the department of Onco anaesthesia and critical care, State cancer institute, GMCH to observe the post-operative analgesia after Cytoreductive Surgeries in patients receiving intrathecal morphine.

Ethical clearance was obtained from the institutional ethics committee prior to commencement of the trial. Based on the selection criteria, 40 patients were selected of ASA 2 scheduled for Cytoreductive Surgeries and were divided into 2 groups of 20 patients each.

Group ITM received 300 mcg of intrathecal morphine along with standard anaesthetic care while placebo control group received the standard anaesthetic care. Injection Fentanyl 2mcg/kg was used in both the groups at the time of induction and Infusion Paracetamol 1gm was used intraoperatively in both the groups. Inf Paracetamol was also used postoperatively 12 hourly in both the groups.

The parameters used in this study were age, weight, heart rate, SBP, DBP, MAP, VAS score for 48 hours. Time of first rescue analgesia.

Analgesic consumption in the first 24 hours, analgesic consumption in the next 48 hours and side effects.

In our study the demographic profile such as age, weight, ASA physical status were comparable in both groups and were statistically insignificant.

In our study the hemodynamic status was assessed in terms of heart rate, systolic blood pressure (SBP), diastolic blood pressure(DBP) and mean arterial pressure (MAP).

There was no statistically significant variation in the hemodynamic status in both the groups ($p>.05$).

There was statistically significant difference ($p<.05$) in favor of ITM with respect to VAS for most part of our study.

There was statistically significant difference in the use of rescue analgesic immediately after the postoperative period at 2hours postoperatively.

1 patient in ITM group (Group1) needed first rescue analgesia at 2nd hour whereas 19 patients needed in Placebo group (Group2) which was statistically significant p-value <0.0001.

It was observed that total analgesic consumption in group 1 was 46 and in group 2 was 114 in 48 hours. Total analgesic consumption in first 24 hours in group1 was 30 whereas in group 2 it was 87 which was statistically significant.

There was no significant adverse effect in both the groups.

Total ICU stay in both the groups were comparable and was not statistically significant

**Keywords:** Intrathecal morphine, Visual analogue score (VAS), Cytoreductive Surgery post-operative rescue analgesics, Total analgesics , Length of ICU stay.



## Introduction

Regardless of several great efforts in developing modern screening, diagnosis and therapeutic strategies, the incidence and mortality of ovarian cancer have not seen any significant change in the last 30years [1,3]. It remains the leading cause of death from gynecologic malignancy with a lifetime probability of developing the disease of 1 in 59.1 Worldwide, approximately 200000 women are annually diagnosed with ovarian cancer2,3 and almost 70% of them are diagnosed at advanced stage

disease 3 With current treatment modalities, the 5-year survival rate ranges from 80–95% for those with organ-confined or early stage disease (International Federation of Gynecology and Obstetrics (FIGO) stage I-II); to 30–40% for those women with advanced disease, FIGO stage III- IV Thus, ovarian cancer is a complex and challenging malignancy [1,4]

Cytoreductive surgeries are major abdominal surgery that includes a broad range of surgical procedures adequate surgical staging procedures including exploration of abdomen, pelvis, peritoneal washings, bilateral salpingo - oophorectomy, hysterectomy, peritoneal biopsies of Cul-de-sac, pelvic walls, paracolic gutters, diaphragm, suspicious areas, omentectomy, appendicectomy, as well as pelvic and para-aortic node dissection upto the renal veins [6]; resulting in severe pain and analgesia requirements. Hence, analgesic strategies should consider patient factors and the surgical procedure.

Patients with immence postoperative pain are associated with increased morbidity, delayed functional recovery and poorer quality of life. Further, suboptimal postoperative analgesia is a risk factor for increased opioid use, opioid dependence and persistent post-surgical pain.

Morphine delivered via the intrathecal rather than the intravenous route has a prolonged duration of action and higher potency [7].

The benefits of intrathecal hydrophilic opioids, compared with intravenous administration, are believed to be caused by a higher potency and a prolonged action, because of a small distribution volume of the CSF and a slow diffusion, respectively. Used as a single bolus technique, intrathecal hydrophilic opioids have an intravenous opioid-sparing effect, facilitate mobilisation and because of a lack of peripheral vasodilation a restrictive fluid management can easily be achieved. These properties may lead to a faster recovery after abdominal surgery [8].

The risks, however, are pruritus, nausea, and late respiratory depression. Especially the fear for the latter has limited the use of intrathecal hydrophilic opioids [9,10],.

**Aims and Objectives**

This study aims to compare the analgesic effect and side effects of intrathecal morphine alone and no intrathecal morphine injection in Cytoreductive Surgery for 24 hours and 48hours postoperatively.

**Primary Outcome:**

1. To compare Visual analogue score (VAS) in patients receiving intrathecal morphine alone and no intrathecal injection in Cytoreductive Surgery for 24 hours and 48 hours postoperatively

**Secondary Outcome:**

1. To compare the use of post-operative rescue analgesics in both the study groups
2. To compare the use of Total analgesics postoperatively in both the study groups in 24 and 48 hours.
3. To compare the incidence of side- effects in both the study group
4. Length of ICU stay.

**Material & Methods**

**Study Area:**

The present randomized clinical trial was conducted in the Department of Onco - Anaesthesia and Critical Care, State Cancer Institute, Gauhati Medical College, Guwahati, after obtaining approval from ethical and scientific committee of institution and written informed consent. Patients with ovarian carcinoma belonging to ASA 2 posted for Cytoreductive Surgeries were taken up for the study over the period of June 2022 – June 2023.

The sample size for this study is 40. The study sample had been divided into two groups each containing 20 patients. 20 patients received intrathecal morphine whereas the other 20 patients received only intravenous analgesics.

**Inclusion Criteria:**

- Patients undergoing Cytoreductive Surgery aged 18–65 years, and with American Society of Anesthesiologists physical status Classe II are to be included in the study.

**Exclusion Criteria:**

- Patients who refuses consent for the study.
- Patients with ASA classification 3 and above.
- Patients with coagulation abnormality or any contra indications for spinal or epidural anaesthesia.
- Patients with drug allergy.
- Patients with decreased respiratory reserve (e.g., chronic obstructive pulmonary disease [COPD], severe obesity, kyphoscoliosis, phrenic nerve palsy)

**Pre–Anaesthetic Check-Up:**

Written and informed consent for willingness to participate in the study was obtained from each subject deemed fit in this assessment prior to inclusion in the study. After institutional ethical clearance and written informed consent, 40 female patients posted for Cytoreductive Surgeries were included in the study. After comprehensive history taking patient's general examination, systemic examination and airway assessment was done.

**Investigations**

The following investigations were done:

TLC, DLC, Hb, platelet count, blood group and cross matching, blood sugar, serum creatinine and blood urea, liver function test, PT/ INR, CXR(PA view), ECG and viral markers.

**Preoperative Preparation Protocol**

Patient kept NPO for at least 6 hours to solid and 2 hours to liquidprior to surgery

Operation theatre was prepared by checking anaesthesia machine, allequipment's and drugs

**Anaesthesia Procedure**

Forty patients were selected randomly and were divided into two groups.

Patient group assignment, drug preparation, and drug administration was provided by a trained anaesthesiologist uninvolved in the rest of the study.

All the participants were explained about the sequence of events in the peri operative period. In the operation theatre patients were positioned in supine position first. Standard monitors that include electrocardiogram, non- invasive blood pressure and pulse oximeter were applied. Vascular access were secured using a 18 G cannula Intravenous fluid was started.

The first group of patients ( i.e ITM group) were to receive intrathecal morphine. The patients were put in sitting position and using strict aseptic condition 300 mcg morphine was injected into the subarachnoid spaceusing a 25 G Quincke's spinal needle at L2- L3 intervertebral space after confirming free flow of CSF. After the intrathecal injection the patients were put in supine position.

In the placebo control group, 1mL of normal saline was injected percutaneously using the 25G needle. The patient were positioned back in the supine position.

For both groups, standardized general anesthesia was administered after the procedure. The patients received pre- medication with inj. Glycopyrolate 0.2 mg , inj. Fentanyl 100 mcg and inj. Ondensetron 4mg. The patients were induced with inj. Propofol at 2mg/kg body weight and then inj. Succinylcholine at 1.5 mg/kg . After that tracheal intubation was done with an endotracheal tube the patient was put on intermediate acting muscle relaxant (inj.Vecuronium at 0.1mg/kg body weight). The patient was then put on mechanical ventilation in the volume control mode and anaesthesia was maintained with oxygen, nitrous oxide and sevoflurane along with intermittent doses of vecuronium. After that under strict asepsis Ultrasound guided Internal Jugular Central Vein cannulation was done. Inf. PCM 1gm was administered. After the procedure was over the patients werereversed from the effects of muscle relaxant using Inj. Neostigmine 2.5mg and Inj. Glycopyrolate 0.5 mg.

The patients heart rate (HR), blood pressure( BP), and visual analogue score(VAS) was recorded and then the patient was shifted to the intensive care unit( ICU).The VAS, HR and BP was recorded every 2 hours for the first 12 hours, then every 4 hours for the next 12 hours. After that the VAS was assessed every 8 hourly for the next 48 hours.

The patients were put on infusion Paracetamol 1g i/v 12 hourly. If the VAS was 4 or more at any time, Inf. PCM 1gm was given as a rescue analgesic ifthe last dose of paracetamol exceeded 4 hours and if not then Inj. tramadol 100mg was given with 100 ml of normal saline.

The total length of stay in the ICU was also noted in both the groups.

**Method of Measurement of Outcome:**

The visual analogue score was assessed at the end of the procedure then every 2 hours for the next 12 hours then every 4 hours for another12 hours then every 8 hours for next 48 hours.
The analgesic consumption in the first 24 hours and then in the next 48 hours was calculated.
The time for the first rescue analgesic was calculated.
The number of side effects in both the groups was calculated.
The total duration of stay in the ICU was calculated in hours.

**Statistical Analysis**

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance using Student's t- test and Chi- Square test.

**Results and Observations**

**Table1: Demographic profileTable 1**

| Parameters | ITM(Group 1) | | PLACEBO(Group 2) | | p-value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Age | 46.60 | 9.63 | 51.55 | 10.92 | 0.137 |
| Weight | 60.80 | 9.58 | 59.55 | 8.82 | 0.670 |

The mean age in group 1 was 46.60 ± 9.63 years and in group 2 was 51.55 ± 10.92 years which is comparable in between the groups.

The mean weight in group 1 was 60.80 ±9.58 kg and 59.55± 8.82 kg ingroup 2. The weight distributions of both the groups are comparable.

Heart rate was compared at different times in both groups. The mean heart rate changes were statistically significant at 2,4,6,8 and 20 hour in both the group. But overall heart rate was concerned and the p value was not significant at any time in the study period.

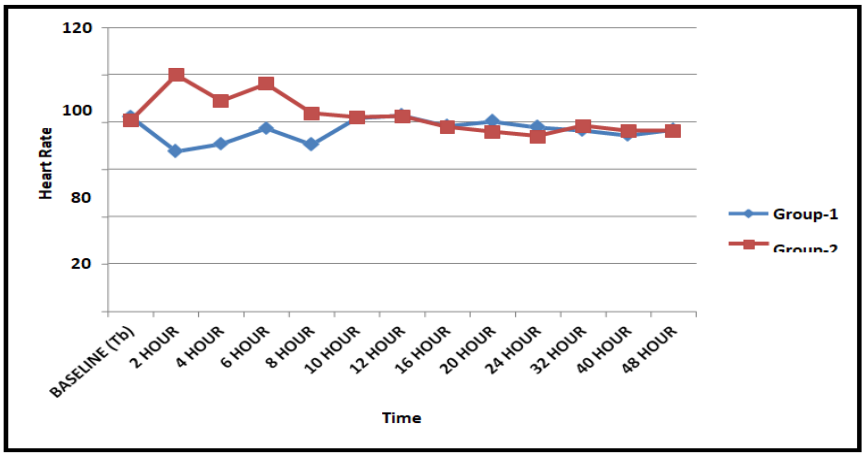


**Fig 2.1**

In our study there was no significant difference between the patients of group 1 and group 2 as far as systolic BP was concerned and the p value was not significant at any time in the study period.

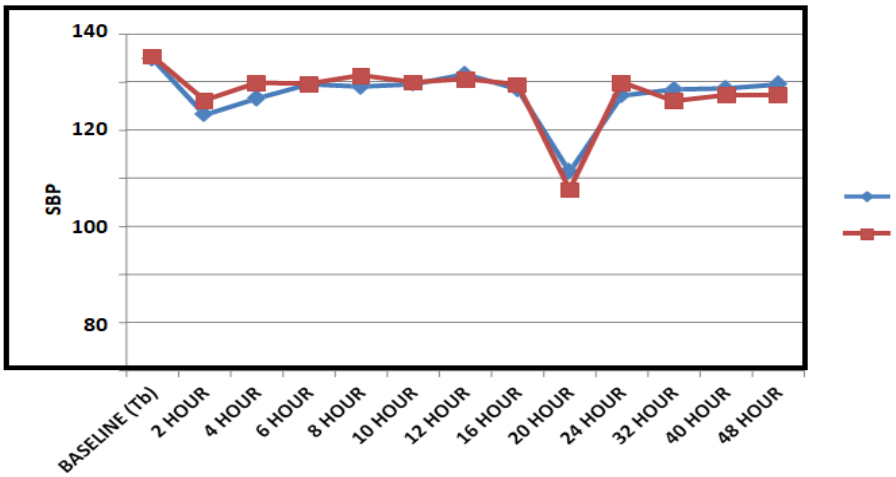


**Fig 3.1**

In our study there was no significant difference between the patients of group 1 and group 2 as far as diastolic BP was concerned and the p value was not significant at any time in the study period.

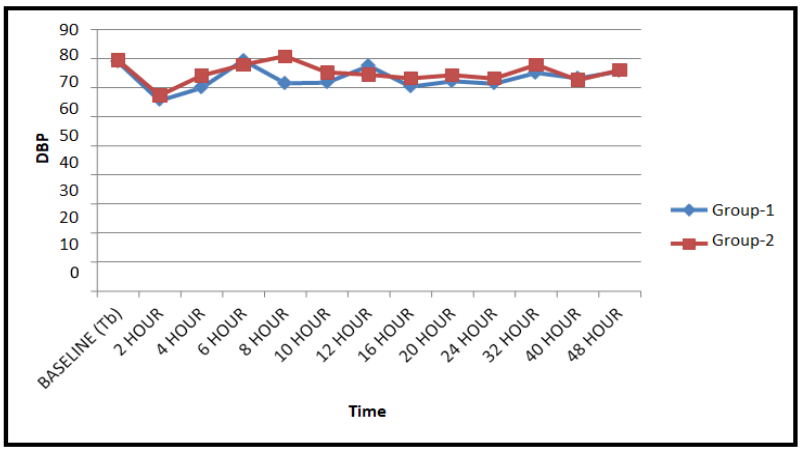


**Fig 4.1**

In our study there was no significant difference between the patients of group 1 and group 2 as far as Mean Arterial Pressure was concerned and the p value was significant only at 4th hour in the study period.

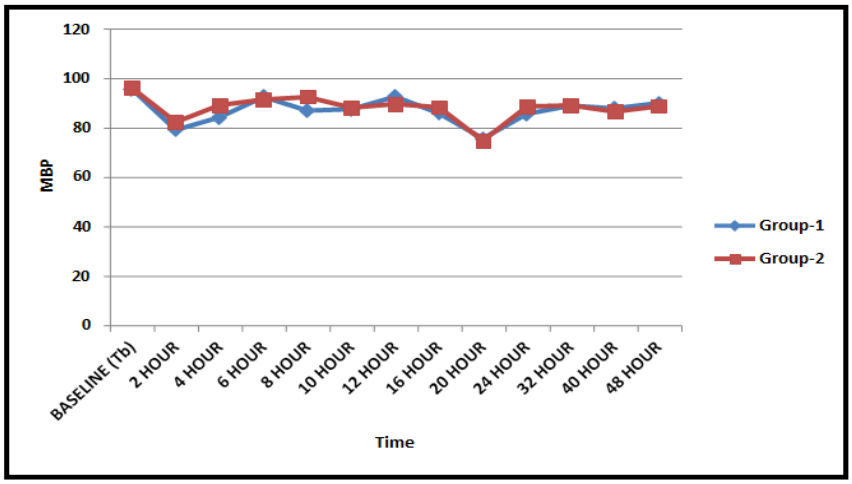


**Fig 5.1**

**Table 6: Visual analogue scale**

| VAS | ITM (Group1) | | PLACEBO (Group 2) | | p-value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| BASELINE (Tb) | 0.45 | 0.76 | 0.20 | 0.52 | 0.233 |
| 2 HOUR | 2.55 | 0.69 | 4.95 | 0.83 | 0.000 |
| 4 HOUR | 1.85 | 0.93 | 4.40 | 0.68 | 0.000 |
| 6 HOUR | 2.40 | 0.50 | 2.85 | 0.37 | 0.003 |
| 8 HOUR | 2.35 | 0.49 | 3.15 | 0.88 | 0.001 |
| 10 HOUR | 2.60 | 0.50 | 5.15 | 1.04 | 0.000 |
| 12 HOUR | 3.45 | 0.69 | 3.10 | 0.79 | 0.142 |
| 16 HOUR | 3.60 | 0.75 | 4.20 | 0.83 | 0.022 |
| 20 HOUR | 3.55 | 0.69 | 3.60 | 0.50 | 0.794 |
| 24 HOUR | 3.45 | 0.51 | 3.00 | 0.32 | 0.002 |
| 32 HOUR | 3.80 | 0.62 | 4.30 | 0.57 | 0.011 |
| 40 HOUR | 3.25 | 0.64 | 3.60 | 0.82 | 0.141 |
| 48 HOUR | 3.00 | 0.00 | 3.00 | 0.00 | - |

The above table shows the comparison of VAS Score at rest between the two groups from 2 hour to 48 hour was observed. There is statistically significant difference ($p<0.05$) between both the groups.

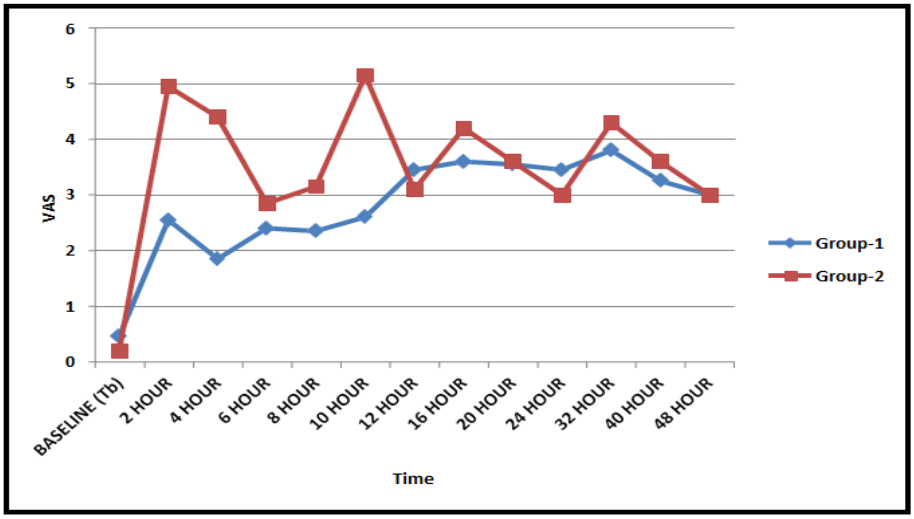


**Fig 6.1**

**Table 7:**

| | ITM (Group 1) | | | PLACEBO(Group 2) | | |
|---|---|---|---|---|---|---|
| | Tramadol | Fentanyl | Paracetamol | Tramadol | Fentanyl | Paracetamol |
| BASELINE (Tb) | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 HOUR | 1 | 0 | 0 | 19 | 0 | 0 |
| 4 HOUR | 0 | 0 | 0 | 0 | 18 | 0 |
| 6 HOUR | 0 | 0 | 0 | 0 | 0 | 0 |
| 8 HOUR | 0 | 0 | 0 | 0 | 3 | 0 |
| 10 HOUR | 0 | 0 | 0 | 0 | 17 | 0 |
| 12 HOUR | 7 | 0 | 0 | 3 | 0 | 0 |
| 16 HOUR | 0 | 9 | 0 | 0 | 9 | 6 |
| 20 HOUR | 0 | 0 | 9 | 0 | 0 | 11 |
| 24 HOUR | 4 | 0 | 0 | 0 | 0 | 1 |
| 32 HOUR | 13 | 0 | 0 | 18 | 0 | 1 |
| 40 HOUR | 3 | 0 | 0 | 8 | 0 | 0 |
| 48 HOUR | 0 | 0 | 0 | 0 | 0 | 0 |

It was observed that total analgesic consumption in group 1 was 46 and in group 2 was 114 in 48 hours of which 1 patient needed analgesic at 2nd hour in intrathecal group and 19 patients required analgesic at 2nd hour in placebo group.

**Table 8:**

| RESCUE ANALGESIA | ITM (Group1) | | PLACEBO(Group2) | | p-value |
|---|---|---|---|---|---|
| | N | % | N | % | |
| 2 HOUR | 1 | 5.00 | 19 | 95.00 | <0.0001 |

**Table 9:**

| RESCUE ANALGESIA | ITM(Group1) | | PLACEBO(Group2) | | p-value |
|---|---|---|---|---|---|
| | N | % | N | % | |
| BASELINE (Tb) | 0 | 0.00 | 0 | 0.00 | - |
| 2 HOUR | 1 | 5.00 | 19 | 95.00 | <0.0001 |
| 4 HOUR | 0 | 0.00 | 18 | 90.00 | <0.0001 |
| 6 HOUR | 0 | 0.00 | 0 | 0.00 | - |
| 8 HOUR | 0 | 0.00 | 3 | 15.00 | 0.2301 |
| 10 HOUR | 0 | 0.00 | 17 | 85.00 | <0.0001 |
| 12 HOUR | 7 | 35.00 | 3 | 15.00 | 0.2308 |
| 16 HOUR | 9 | 45.00 | 15 | 75.00 | 0.1069 |
| 20 HOUR | 9 | 45.00 | 11 | 55.00 | 0.7518 |
| 24 HOUR | 4 | 20.00 | 1 | 5.00 | 0.3401 |
| 32 HOUR | 13 | 65.00 | 19 | 95.00 | 0.0177 |
| 40 HOUR | 3 | 15.00 | 8 | 40.00 | 0.0769 |
| 48 HOUR | 0 | 0.00 | 0 | 0.00 | - |

The need for rescue analgesia was statistically significant at 2nd, 4th, 10th,32nd and 40th hour

**Table10: Side Effects**

| | ITM | | PLACEBO | |
|---|---|---|---|---|
| SIDEEFFECT | N | % | N | % |
| Vomiting | 0 | 0 | 0 | 0 |
| Purities | 0 | 0 | 0 | 0 |
| Hypotension | 0 | 0 | 0 | 0 |
| Limb weakness | 0 | 0 | 0 | 0 |
| Respiratory Depression | 0 | 0 | 0 | 0 |

It was observed that there were no noted adverse effects in both the groups.

**Table11: ICU stay**

| Duration of ICU Stay | ITM | | PLACEBO | | P-VALUE |
|---|---|---|---|---|---|
| | MEAN | SD | MEAN | SD | |
| DAYS | 3.60 | 0.50 | 3.65 | 0.49 | 0.752 |

Total ICU stay was comparable in both the groups and was notstatistically significant.

**Discussion**

Cytoreductive surgery is the surgery of choice for Ovarian Carcinoma. Cytoreductive surgeries are major abdominal surgery encompasses a broad range of surgical procedures [2]. Effective pain control is an essential requirement post operatively for better overall recovery, early ambulation, better pulmonary function and early discharge from hospital. [3] But in order to achieve all these patient's safety should also be kept in mind and hence the side effects of an analgesic procedure should be kept in mind. The aimof this study was to compare the post-operative analgesic effects as well as the effects on overall recovery with intrathecal morphine over the intravenous analgesic technique.

Following intrathecal administration, all opioids produce analgesia, at least in part, by a spinal mechanism [10].

Morphine delivered via the intrathecal rather than the intravenous route hasa prolonged duration of action and higher potency. [9] No consensus on the optimal dose of intrathecal morphine exists [9]

This open label randomized trial was conducted in the Department of Onco- Anesthesia and Critical Care, State Cancer Institute, Guwahati Medical College and Hospital from June 2022 to June 2023. Total of 40 patients for Cytoreductive Surgery was taken for the study. They were divided into two groups of 20 patients each. One group (ITM group) received intrathecal morphine while the other group (Placebo group) received intravenous multimodal analgesia.

In our study the demographic profiles (age, weight), ASA status, type of surgery were comparable and statistically insignificant.

There is a statistically significant difference ($p<.05$) in favor of ITM group with respect to VAS score for most part of our observation. This result is in accordance to a multi centric double-blind, randomized controlled trial at two tertiary hospitals in Australia conducted by IK. Pirie, M. A. Doane, B. Riedel et al. They concluded that total oral opioid requirement until postoperative day 3 were less in the intrathecal morphine group compared to control group where intravenous analgesics was used. This was in accordance to our study. [11]

In April 16, 2022 a pilot randomized control study was done by Amorn Vijitparan and Nussava Kiltikunakorn where the comparison between intrathecal morphine and intravenous patient controlled analgesia for pain control after video-assisted thorascopic surgery was done. The result showed that post-operative pain scores in ITM group were significantly lower than control group. This was in accordance to our study.

Most studies realized a reduction in pain scores and narcotic use during the first 24 hrs postoperatively. This data was strongly demonstrated and quantified in the meta-analysis by Koning, Klimek et al. (2020) across all major abdominal surgeries, in the colorectal population by Young et al. (2021), in the laparoscopic population by Pirie, Doane et al. (2022) and Koning et al. (2018), in the prostatectomy population by Koning, de Vliegeret al. (2020) and Bae et al. (2017), in the hepato-pancreato-biliary surgery population by Tang et al. (2020), and in the gynecologic population by Selvam et al. (2018) [11]

Their study was in accordance to our study where the total rescue analgesic consumption in the first 24 hours is significantly less in ITM group as compared to placebo control group. 1 patient in ITM group required rescue analgesia after 2 hours, 7 patients required rescue analgesia after 12 hours, 9 patients required rescue analgesia at 16 hours, 9 patients needed at 20 hours .

In our study it was observed that total analgesic consumption in the intrathecal group was 46 and in the placebo group was 114 in 48 hours of which 1 patient needed analgesic at $2^{nd}$ hour in intrathecal group and 19 patients required analgesic at $2^{nd}$ hour in placebo group.

Total analgesic consumption in first 24 hours in intrathecal group was 30 whereas in placebo group it was 87.

In our study the first rescue analgesia was needed at $2^{nd}$ hour.1 patient in ITM group(Group1) needed first rescue analgesia at $2^{nd}$ hour whereas 19 patients needed in Placebo group(Group2) which was statistically significant p-value $<0.05$.

The need for rescue analgesia was statistically significant at $2^{nd}$, 4th, 10th, 32nd and $40^{th}$ hour. No adverse effects were noted in both the groups. Total stay in the ICU was comparable and was not statistically significant.

**Conclusion**

Intrathecal opioid administration is a great analgesic technique since the drug is injected directly into the CSF, close to the structures of the central nervous system where the opioids act. From

our study we can conclude that low dose of intrathecal morphine 300mcg provides adequate analgesia with lower VAS, stable hemodynamic profile and better safety profile along with a lesser consumption of rescue analgesic in the first 24 and 48 hours also a decrease in total analgesic consumption and a reduction in the length of stay in the ICU as compared to only intravenous analgesics.

From our study we conclude that intrathecal morphine reduces intraoperative and postoperative opioid consumption, pain scores and length of ICU stay after cytoreductive surgeries and henceforth we feel that this technique should be used more frequently for postoperative pain management in cytoreductive surgeries.

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