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Comparative Evaluation of Low Dose Intrathecal Morphine versus Multimodal Analgesia in Patients Undergoing Abdominal Surgeries under General Anaesthesia A Randomized Double Blinded Study

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Abstract
Aim Of The Study*: To evaluate the effect of preservative free morphine 0.5mg administered intrathecally , on intraoperative anesthetic requirement and post operative analgesia in patients undergoing laparotomies under general anesthesia compared with multimodal analgesia during the 1st 24 hours of postoperative period.*
Materials And Methods: *50 patients of ASA physical status I,II and III undergoing both upper and lower abdominal surgeries under general anesthesia are categorized into one of two groups, Group M –Morphine study group and Group C – Control group. In both study and control Group routine General anesthesia was administered. In Group M, 0.5mg morphine given intrathecally before general anaesthesia. The parameters studied were intraoperative hemodynamics, post operative pain score and analgesic requirement,post operative hemodynamics, intra operative and post operative complications.*
Results : *The number of demand analgesia in 24 hours is 1.56 in Group – M vs 4.2 in Group- C and it is statistically significant (p=0.0002) . Post operative visual analog score (VAS) in Group-M was 4.64 vs 5 in group – C. But it was highly significant at 2,4,8,12,20 hours and .However, it was not significant at postoperative zero hours, 14,16,24 hours. Postoperative Ramsay sedation scale(RSS) is 2.16 in group – M ,1.6 in Group – C ,this is statistically significant (P=0.0156). The postoperative heart rate in group –M vs Group – C are 85 ± 12.7 and 101 ± 13.9 respectively and it statistically significant (p=0.0002) .The post operative mean arterial pressure (MAP) is 89 ± 15.7 group- M vs 104 ± 14.3 Group - C which is statically significant (P=0.0012).*
Conclusion *: Intrathecal morphine produced better postoperative analgesia and sedation. Intrathecal morphine group demonstrated lesser amounts of analgesic and rescue analgesic requirement during the postoperative period. Intrathecal morphine produced better hemodynamic stability in the postoperative period. Intrathecal morphine produced side effects in the form of nausea, vomiting, hypotension and bradycardia but not statistically significant.*

I. Introduction

Opium means juice, from Greek word. Morphine is named after Greek god of dreams, Morpheus Opioid refers to drugs derived from opium both natural and synthetics. Narcotic refers to morphine and like analgesics.Morphine can be used as spinal analgesic ,Epidural analgesic .Despite the high efficacy, it was not widely used because of high incidence of respiratory depression and somnolence, It was due to high doses ,rather than route of administration . Gwirtz and associates reported high patient satisfaction and low incidence of side effects and complication of morphine over 6000 patients.

Therefore, this study has been undertaken to analyze the effect of intrathecal morphine as more cost effective analgesic when compare to multimodal analgesia

II. Aim Of Study

To evaluate the effect of preservative free morphine 0.5mg administered intrathecally, on intraoperative anesthetic requirement and post operative analgesia in patients undergoing laparotomies under general anesthesia compared with multimodal analgesia during the 1st 24 hours of postoperative period.

The following parameters were studied

1. Intra operative hemodynamic
2. Post operative pain score and analgesic requirement
3. Post operative hemodynamic
4. Complications: Both intra operative and post operative period

III. Materials And Methods

This study was conducted at Coimbatore Medical College Hospital, in the general surgical operation theater.

1. The study was done after getting Institutional Ethical Committee approval
2. Written informed consent were obtained from all patients included in the study

All patients were explained about the procedure and visual analog scale(Pain score) 10cm scale so that it can be effectively used by the patient during the post operative period.

Inclusion criteria	**Exclusive Criteria**
1. A.SA I,II,III patients	1.patient refusal
2. Those patients who are undergoing upper and lower abdominal surgeries	2.Contraindication to subarachnoid block
	3. Hypersensitivity to study group
	4. Difficult airway MMS**>3
	5. Hepatic and renal dysfunction

50 patients of ASA physical status I,II and III undergoing both upper and lower abdominal surgeries like partial Gastrectomy ,open cholecystectomy, incisional hernia, Hemicolectomy and laparotomy under general anesthesia .

The patients are categorized into one of two groups.

Group M – Morphine – study group

Group C – Control group

All patients were assessed preoperatively using standard protocols and underwent preoperative evolution .All patients were premeditated with T.alprazolam,T.Ranitidine 150mg P.O.the night before surgery and on the day of surgery 2hours before operation P.O, with sips of water.

Preservative free morphine sulphate 10mg/ml is diluted to 10ml with sterile normal saline

In study Group M patients were hooked on monitors E.C.G, Pulse oximetry and Non invasive BP.Two IV access with 18G IV cannula was obtained .500ml of normal saline was preloaded. Patients was turned right lateral position .Patient back was painted with antiseptic solution and draped. Morphine was taken in 0.5 mg diluted to 1 cc with normal saline .Subarachnoid block was done with 25G Quinckie spinal needle at L3-L4 ISS after confirming free flow of CSF ,1ml of preservative free morphine 0.5mg was administered intrathecally and patient turned supine position and observed for 10min before induction of GA. Preoxygenation done for 3mins.

In both study and control Group Routine General anesthesia was administer with Inj.Glycopyrrolate 0.2mg +Fentanyl 2µg/kg i.v., and Induction with Inj.Thiopentone 5mg /kg + suxamethonium 2mg/kg after 60 seconds patient incubated with 8 or 8.5 mm cuffed ETT orally for male,7 or 7.5 mm orally in female patients .All patients were catheterized to monitor urine output. Relaxant Inj.Vecuronium 0.12 mg/kg given IV .Maintains with oxygen 50% with Nitrous oxide with volatile agent isoflurane 1%.IV fluids were given according to body loss and 3rd space loss .Vitals were recorded every 5minutes until the end of surgery PR, BP,SPo2.Injection Diclofenac sodium 75mg IV infusion was started after one hour of surgery in both groups .Fentanyl 20µg IV top up per hour. At the End of surgery after replacing blood losses and fluids patient was reversed with Inj.Neostigmine 0.05 mg/kg+ Glycopyrolate 10µg/kg.

After through suctioning and good attempts patient was extubated on table if hemodynamically stable. Patient was shifted to Surgical ICU and monitored by concerned anesthesia PG .All patients were given oxygen by venti mask 4 liter /min and 30° Head up was given.

Pain assessed by visual analog scale (VAS).every hour until 4'hour and thereafter every 2' hours for 24 hours .

Group	Group M – Morphine	Control Group
If VAS >4	Inj. Diclofenac 75mg im	Inj.Diclofenac 75mg Im b.d and inj.Tramadol 100 mg i.v. t.d.s
rescue analgesic	inj.Fentanyl 20 µg titrated to response	inj.Fentanyl 20 µg titrated to response

Recovery characteristics include VAS score, Ramsay sedation scale, postoperative HR, BP, saturation ,complication and effects of opioids were monitored and noted .

The other parameters monitored in the post operative period included

1. Time for 1st demand analgesia,
2. No. of Analgesia doses in 1st 24hours
3. No of NSAID doses in 1st 24 hours
4. No of Rescue analgesic doses in 24 hours ,

The Complication monitored included

1. Retention of urine
2. Respiratory depression .It is defined as a respiratory rate < 8 / min and or oxygen saturation

< 90 %.This was planned to be managed with bag and mask ventilation or intubation and I.P.P.V. if necessary naloxone 0.2 mg IV every 5-10 mins till normal breathing pattern was established

3. Nausea and vomiting managed with Inj.ondansetron 8 mg intravenously
4. Pruritis
5. Hypotension
6. Bradycardia
7. **Ramsay Sedation score (RSS)**. It has six scores

1. Anxious and agitated or restless or both .
2. Cooperative oriented and tranquil
3. Responds to commands only
4. Asleep with brisk response to light glabellar tap or loud auditory stimulus.
5. Asleep with sluggish response to stimulus.
6. Asleep with no response to Stimulus.

A sedation score greater than 4' was considered significant and observed for 24' hours and then shifted to post operative ward .The patient study was completed after 24 hours of intrathecal morphine.

Study.A total of 50 cases each were randomly allocated to one of the following two groups via Group – M(Morphine) and Group – C(Control).The Information collected all the cases were recorded in a Master Chart. Data analysis was done with the help computer using Epidemiological Information Package (EPI 2002).

Using this software, frequencies, Percentages, means, Standard deviation, Chi square and 'p' values were calculated.'p' values less than 0.05 is taken to denote significant relationship.

IV. Observation & Results

The study was conducted at Coimbatore Medical College Hospital .50 patients were included in double blind randomized control study.

Age Group	**Morphine Group**		**Control Group**	
	No	**%**	**No**	**%**
up to 20yrs	1	4	1	4
21-30	5	20	7	28
31-40	6	24	6	24
41-50	7	28	5	20
51-60	3	12	5	20
above 60	3	12	1	4
Total	25	100	25	100
Mean	41.0 years		39.2 years	
SD	13.8 years		12.6 years	
'p'value	0.6835 Not significant			

Table 2 : Sex

Sex	**Morphine Group**		**Control Group**	
	No	**%**	**No**	**%**
Male	14	56	15	60
Female	11	44	10	40
ToTal	25	100	25	100
'p'value	0.7767 Not significant			

The time for 1st demand analgesia in the postoperative period in Group – M is 13.8 hours and in Group - C is 1 hour and statistically significant (p=0.00079).

Table 3 : Analgesic demand

Drug use	**Morphine Group**		**Control Group**		**'p'value**
	No.	**%**	**No.**	**%**	
Time for I PT analgesic demand (in hours)	13.8	11.9	1.0	1.0	**0.0079 Significant**
Number of analgesic demand in 24 hours	1.56	2.31	4.2	2.93	**0.0002 Significant**
Total NSAID used in 24 hours	0.44	0.51	-	-	-
Inj. Fentanyl used in 24 hours((µg)	1.1	1.94	86	72.6	**0.0003 Significant**

The number of demand analgesia in 24 hours is 1.56 in Group – M vs 4.2 in Group- C and it is statistically significant (p=0.0002)The rescue analgesia Inj.Fentanyl used in-Groups – M is 1.1 vs 86 in Group – C and it is statistically sighnificants (p=0.0003).

The Intraoperative systolic BP was 124 in Group - M and 125 in Group – C and statistically not significant.

Intra operative diastolic B.P

Intra operative diastolic BP was compared between both groups had (80 group-M and Group – C 82) and p value as 0.39 and not significant.

Intra operative mean arterial B.P

The mean arterial pressure is not significant between both groups and group – M had 94 ± 10.8 and in Group – C 96 ± 12.6 and p value 0.5527. But is significant at 90^{th} min (P=0.0262). Probably it is associated with onset of action of IT morphine.

Intra operative pulse Rate

Intra operative pulse rate in group –M was 90± 14 vs 91 ± 16.9 in Group – C and it is statistically not significant.

Post operative VAS

Post Op. Vas at	M Group		Control Group		'p'value	Significance
	Mean	SD	Mean	SD		
0 hours	4.64	1.41	5.0	1.41	0.3609	Not Significant
2 hours	4.12	1.2	5.21	0.88	**0.0002**	**Significant**
4 hours	3.76	0.88	4.6	0.76	**0.0009**	**Significant**
8 hours	3.8	0.76	4.4	0.76	**0.0055**	**Significant**
10 hours	3.8	0.71	3.92	0.49	0.2868	Not Significant
12 hours	3.6	0.58	4.04	0.61	**0.0137**	**Significant**
14 hours	3.72	0.54	3.76	0.66	0.9177	Not Significant
16 hours	3.84	0.47	3.96	0.45	0.3609	Not Significant
18 hours	3.84	0.47	3.88	0.53	0.8	Not Significant
20 hours	3.84	0.47	4.08	0.76	0.199	Not Significant
22 hours	3.88	0.44	4.4	0.65	**0.0017**	**Significant**
24 hours	3.92	0.49	3.84	0.55	0.5704	Not Significant

Post operative visual analog score (VAS) in Group-M was 4.64 vs 5 in group – C. But it was highly significant at 2,4,8,12,20 hours and .However, it was not significant at postoperative zero hours, 14,16,24 hours. Intrathecal Morphine seems to have a certain lag in onset of analgesia.

Post operative RSS

Post Op. Vas at	M Group		Control Group		'p'value	Significance
	Mean	SD	Mean	SD		
0	2.16	0.8	1.6	0.76	**0.0156**	**Significant**
2	2.32	0.47	1.56	0.65	**0.0001**	**Significant**
4	2.28	0.46	1.56	0.58	**0.0001**	**Significant**
6	2.32	0.48	1.68	0.56	**0.0002**	**Significant**
8	2.28	0.46	1.68	0.56	**0.0003**	**Significant**
10	2.24	0.52	1.88	0.44	**0.0124**	**Significant**
12	2.24	0.44	1.92	0.4	**0.0113**	**Significant**
14	2.24	0.44	2.0	0.29	**0.0281**	**Significant**
16	2.24	0.44	2.04	0.2	**0.0437**	**Significant**
18	2.24	0.48	2.04	0.2	**0.0107**	**Significant**
20	2.32	0.49	2.04	0.2	**0.0051**	**Significant**
22	2.32	0.48	2.04	0.2	**0.0107**	**Significant**
24	2.28	0.46	2.04	0.2	**0.0219**	**Significant**

Postoperative Ramsay sedation scale(RSS) is 2.16 in group – M ,1.6 in Group – C ,This is statistically significant (P=0.0156).

Post Operative Heart Rate.

Post heart rate at hours	M Group		Control Group		'p'value	Significance
	Mean	SD	Mean	SD		
0	85	12.7	101	13.9	**0.0002**	**Significant**
2	80	10.2	100	11.4	**0.0001**	**Significant**
4	76	9.8	99	12.2	**0.0001**	**Significant**
8	76	11.3	99	10	**0.0001**	**Significant**
12	79	11.5	99	11.3	**0.0001**	**Significant**
16	78	9.1	100	10.1	**0.0001**	**Significant**
20	78	8.2	100	9.6	**0.0001**	**Significant**
24	77	8.5	102	8.8	**0.0001**	**Significant**

The postoperative heart rate was In group –M vs Group – C are 85 ± 12.7 and 101 ± 13.9 respectively and it statistically significant (p=0.0002) during the post operative period .

Post operative systolic B.P

Post operative SBP at hours	M Group		Control Group		'p'value	Significance
	Mean	SD	Mean	SD		
0	116	23.4	138.7	22.2	**0.0018**	**Significant**
2	113.0	21.6	135.2	22.2	**0.0033**	**Significant**
4	111.3	22.2	140.3	17.5	**0.0001**	**Significant**
8	109	22.4	140.2	16.3	**0.0001**	**Significant**
12	110.4	20.5	141.5	18.1	**0.0001**	**Significant**
16	109.2	19.8	138.4	18.4	**0.0001**	**Significant**
20	107.5	18.4	139.4	18.7	**0.0001**	**Significant**
24	107.2	17	137.8	17.2	**0.0001**	**Significant**

Post operative systolic BP was 116 ± 23.4 in Group – M vs 138 ± 22 in control Group which is statistically significant p =0.0018.

Post operative Diastolic B.P

Post operative DBP at hours	M Group		Control Group		'p'value	Significance
	Mean	SD	Mean	SD		
0	75.4	12.7	87.1	11.7	**0.0019**	**Significant**
2	76	13.7	85.8	9.4	**0.0145**	**Significant**
4	73.9	13.2	86.6	8.3	**0.0001**	**Significant**
8	72.9	12.3	89	9.8	**0.0001**	**Significant**
12	73.3	11.1	88.1	9.4	**0.0001**	**Significant**
16	72	9.8	87.1	7.5	**0.0001**	**Significant**
20	71.2	10.2	86.6	8.4	**0.0001**	**Significant**
24	71	9.6	85	6.3	**0.0001**	**Significant**

Post operative Diastolic BP was 75.4 ± 12.7 in group – M vs 87.1 ± 11.7 in control group which is statistically significant p=0.0019.

Post operative MAP

Post operative MAP at hours	M Group		Control Group		'p'value	Significance
	Mean	SD	Mean	SD		
0	89	15.7	104	14.3	**0.0012**	**Significant**
2	88	16.1	102	12.4	**0.0049**	**Significant**
4	86	15.9	104	10.1	**0.0002**	**Significant**
8	85	15.3	107	10.9	**0.0001**	**Significant**
12	86	13.9	106	10.8	**0.0001**	**Significant**
16	84	12.4	104	10.1	**0.0001**	**Significant**
20	83	12.4	104	10.3	**0.0001**	**Significant**
24	83	11.7	103	8.8	**0.0001**	**Significant**

The post operative mean arterial pressure (MAP) is 89 ± 15.7 group- M vs 104 ± 14.3 Group - C which is statiscally significant (P=0.0012)

Table : Complications

Complications	Morphine Group		Control Group	
	No.	%	No.	%
Nausea	11	44	9	36
Vomiting	11	44	9	36
Respiratory Depression	3	12	-	-
Pruritis	11	44	5	20
Desaturation	1	4	-	-
Hypotension	3	12	-	-
Bradycardia	2	8	-	-
Total cases with complications	19	76	12	48
Total cases without complications	6	24	13	52
'p'value	0.0804 Not significant			

There was no statically significant difference in the complication between 2 groups. However Nausea and vomiting was more in the IT Morphine group (11 vs 9).Desaturation, Pruritis , bradycardia and hypotension was also more In the morphine Group .these findings may be clinically relevant although statistical analysis did not reveal any significant difference

V. Discussion

1. Analgesia

Post operative (VAS) score in Group – M was 4.64 vs 5 in Group – C. But it was highly significant at 2,4,8,12,20 hours and non significant at post operative 0,14,16,24 hours .Intrathecal morphine has superior post operative analgesia effect .Gwirtz KH ,Young JV, Byers RS,Alley C, Levin K, Walker SG, Stoelting RK found in their retrospective study intrathecal morphine analgesia was superior for acute postoperative pain in 5969 surgical patients studied at Indian University Hospital undergoing major urologic,orthopedic,general/vascular thoracic and gynecology surgeries .The findings in our study are in agreement with this study.Jean-Michael Devys,Anne Mora,Benoit Plaud et al in their study found IT morphine 0.4mg I 60 adult patient undergoing major abdominal surgery produce VAS scores that were lower in the IT morphine group for the first 48 hours . This is totally in agreement with finding of this study

Time For Demand Analgsia And Doses Of Rescue Analgesia

The number of demand analgesia in 24 hours is 1.56 in group – M vs 4.2 in group – C and it is statically significant (p=0.0002).It is Fentanyl used in group - M is 1.1 vs 86 in group – C and it is statically significant (p=0.0003).

Andrew et al studied the efficacy and safety of low dose intrathecal morphine for post operative analgesia in children. The time for demand analgesia by patient required Opioid administration(parental or oral) was approximately 8 hours .our study has similar findings established the efficacy of IT morphine

Intraoperative And Post Operative Hemodynamics

Intra operatively SBP,DBP,MAP,HR,SaO2 there was no difference between both Groups M and C. Post operatively group – M demonstrated significantly stable hemodynamics due to superiors and stables pain control .

ASK Kwan , BB.Lee, T.Brake et al in their study used 0.2 mg IT morphine to 2.2ml of hyperbaric bupivacaine in patients undergoing hip surgeries no alterations in hemodynamics both intra-operative and post operative period .the finding in our study agree with these conclusions.

Post Operative Complication:

Nausea and vomiting was more in IT Morphine group (11 vs 9). Desaturation ,Pruritis , bradycardia and hypotension was also more in Group-M Although these findings may be clinically relevant but statistical did not reveal any significant difference. Glyan CG et al (1979) and Davies GK et al (1980) reported respiratory depression following spinal morphine .in our study 2 patient with hypoventilation and 1 patient developed desaturation but were easily managed by oxygen supplementation. Reiz and Westberg (1980) and Yaksh TL (1981) and samii j, chanin M and Viars P (1981)reported pruritus and urinary retention after intrathecal opioids ,Our study recorded pruritis but urinary retention could not be assessed since all patients continued to have their bladder catheterized during the study period. Ganesh A,K.M.A Cucchiaro studied the effect of low dose (4-5µg/kg) intrathecal morphine and found the incidence of Nausea or vomiting pruritus and urinary retention was 32%,37% and 6% respectively. The findings in our study are in concurrence with these studies.

Summary

1. Intrathecal morphine produced better postoperative analgesia as shown by lower VAS scores.
2. Intrathecal morphine group demonstrated lesser amounts of analgesic and rescue analgesic requirement during the postoperative period.
3. Intrahecal morphine produced better hemodynamic stability in the postoperative period and was associated with lower heart rates.
4. Intrahecal morphine produced more side effects in the form of nausea, vomiting, hypotension and bradycardia. Although not statistically significant seems to be clinically relevant. A larger study sample may have revealed statistical significance.
5. Intrathecal morphine group patients had better sedation as shown by RSS.
6. All the side effects produced by IT morphine were easily manageable and did not contribute to any increase in mortality or morbidity.
7. IT morphine did not seem to produce any significant changes in the hemodynamics during intraoperative period. This may be related to rostral spread of the drug.
8. IT morphine does not require any complex instrument or procedure for administration. It is cost effective.

VI. Conclusion

Intrathecal morphine produced better postoperative analgesia and sedation. Intrathecal morphine group demonstrated lesser amounts of analgesic and rescue analgesic requirement during the postoperative period. Intrathecal morphine produced better hemodynamic stability in the postoperative period. Intrathecal morphine produced side effects in the form of nausea, vomiting, hypotension and bradycardia but not statistically significant.

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