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Evaluation of postoperative acute opioid induced hyperalgesia/acute tolerance after Intrathecal administration of fentanyl in patients undergoing cesarean delivery - A randomised control study

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Introduction

Spinal anaesthesia for caesarean delivery has become popular because of addition of opioid to local anaesthetic, which will provide better postoperative analgesia. The advantages of spinal anaesthesia include the simplicity of technique and the rapid onset of anaesthesia. Opioids act as agonists at stereo-specific opioid receptors at presynaptic and postsynaptic sites in the central nervous system. Existence of the opioid in the ionized state appears to be necessary for strong binding at the anionic opioid receptor site. The principal effect of opioid receptor activation is a decrease in neuro transmission at presynaptic site.

The principal effect of opioid receptor activation is a decrease in neurotransmission at presynaptic site. The intracellular biochemical events initiated by occupation of opioid receptors with an opioid agonist are characterised by increased potassium conductance leading to hyperpolarization, calcium channel activation, or both, which produce an immediate decrease in neurotransmitter release.

Opioid receptors exist on the peripheral ends of primary afferent neurons and their activation may either directly decrease neurotransmission or inhibit the release of excitatory neurotransmitter such as substance P.

Keywords: Opioid, PCA, VAS.

Aim

To assess development of acute tolerance or opioid hyperalgesia in patients undergoing caesarean section with intrathecal fentanyl added to spinal anaesthesia and intraoperative opioids, to assess duration of block and hemodynamic variation and to assess adverse effects like Nausea, vomiting.

Materials and methods

90 patients aged between 22-40 for elective caesarean section at AJIMS Mangaluru were considered, divided into three groups.

Group 1 received: intrathecal hyperbaric bupivacaine 10mg, fentanyl 25mcg and IV morphine 3mg after extraction of baby; group 2 received intrathecal injection of hyperbaric bupivacaine 10mg, IV morphine 3mg after extraction of baby and group 3(control) received: intrathecal bupivacaine 10mg, fentanyl 25 mcg. All patients in post op received i.v. morphine through patient-controlled analgesia (PCA). The analgesia provided was subjectively assessed using the VAS scores.

Selection criteria

Inclusion Criteria: Patients posted for elective caesarean section under spinal anaesthesia,

Patients belonging to ASA 1 or ASA 2, pregnant females in the age group 22-40 years and Patients with full term singleton pregnancy (37 weeks of gestation)

Exclusion Criteria: Patients belonging to ASA 3 and above, Patients with morbid obesity (BMI more than 40kg/m2), planned postpartum tubal ligation and previous adverse reaction to opioid medications or history of chronic opioid use.

Statistical analysis

Sampling and sample size: Based on the key article-―Intrathecal fentanyl added to bupivacaine and morphine for cesarean delivery may induce a subtle opioid tolerance‖ by authors B. Carvalho, D.R. Drover, Y. Gino Sar, S.E. Cohen, E.T. Riley published in the year 2011with an alpha error of 5% , power of 80 % , an average standard deviation of 6 , the minimum difference in values which will make clinically relevant impact (to be decided by the clinician)of 5 we arrive at a sample size of 23 per group . Assuming a dropout of 10% of subjects we consider a total of 30 patients per group for analysis.

If statistical analysis reveals $P > 0.05$, we would reject the null hypothesis. Statistical analysis was done through Minitab 17 and Graph Pad Prism (version 7, inc. Belgium). Data were checked for its distribution of normality prior to any tests aliedto analysis. The data's analysed are parametric or non-parametric using Kolmogorov Smirnov test or any similar tests of normality, and measured for skewness and kurtosis. Data was presented as frequencies, proportions or as mean and standard deviations. Demographic data and study parameters comprising numerical data with mean (standard deviation) were analysed using One way ANOVA; unpaired or paired, accordingly.

The data recorded at various intervals (baseline, 1st hour; 8th, 16th, 24th hours) are studied with in the group by repeated measures of ANOVA with multiple comparisons with Bonferroni corrections or any other similar tests as appropriate, were used.

If non-parametric data is found with respect to procedure-based groups, the counter part of above-mentioned statistical tests were used. Categorical data are analysed using chi-square test or Fisher exact tests as appropriate. A Kaplan-mier survival analysis was followed to compare the time to request first analgesia dose of paracetamol between the groups.

The P value less than 0.05 was considered as minimum value for statistical significance

< 0.05 – suggestively significant *, <0.01 – moderately significant **, <0.001- highly significant ***

Observation and Results

Comparison of age : Age was comparable between the two groups. The mean age for Group 1 was 28.43±3.396, Group 2 was 29.57±2.982 and Group 3 was 29.30±4.226.

Table 1:

Demographic data	Group1(n=23)		Group2(n=23)		Group3(n=23)		P
	Mean	SD	Mean	SD	Mean	SD	
AGE	28.43	3.396	29.57	2.982	29.30	4.226	0.535

GRAPH 1a: Comparison of age between the groups

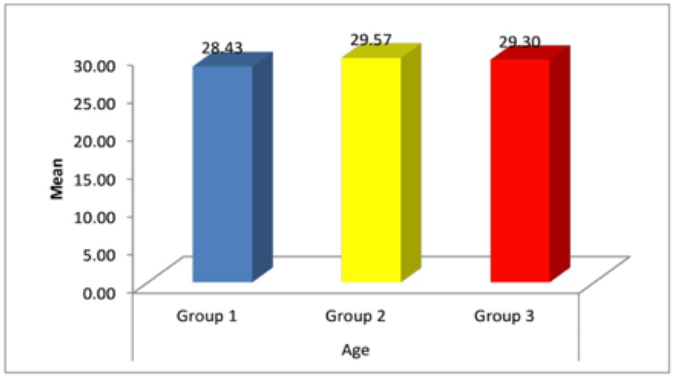
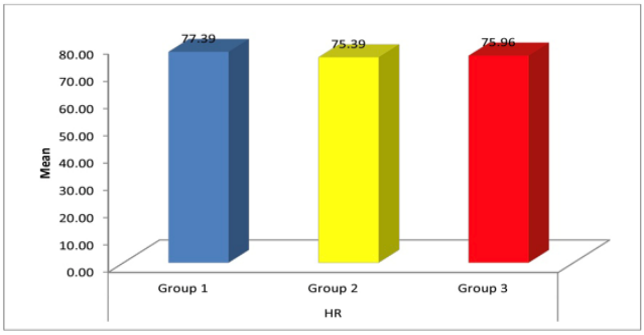


Table 2: Comparison of heart rate

Demographic data	Group1(n=23)		Group2(n=23)		Group3(n=23)		P
	Mean	SD	Mean	SD	Mean	SD	
HR	77.39	6.444	75.39	5.679	75.96	5.973	0.515

GRAPH 2 a : Comparison of HR between the groups

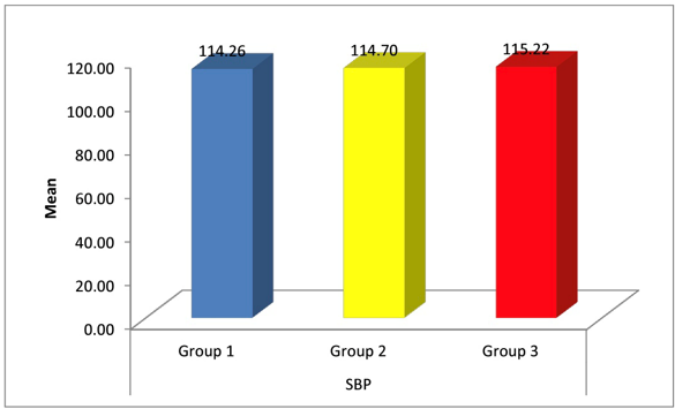


HR was comparable between the two groups. The mean HR for Group 1 was 77.39±6.44, Group 2 was 75.39±5.679 and Group 3 was 75.96±5.973.

Table 3: Comparison of SBP

Demographic data	Group1(n=23)		Group2(n=23)		Group3(n=23)		P
	Mean	SD	Mean	SD	Mean	SD	
SBP	114.26	9.112	114.70	9.584	115.22	8.712	0.939

Graph 3:

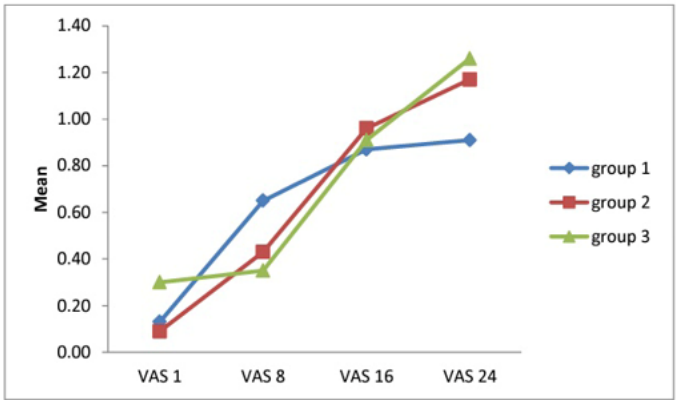


SBP was comparable between the two groups. The mean SBP for Group 1 was 114.26±9.112, Group 2 was 114.70 ± 9.584 and Group 3 was 115.22±8.712.

Table 4: Distribution of Vas scores

VAS SCORE(Hours)	Group1 (n=23)		Group2 (n=23)		Group3 (n=23)		P
	Mean	SD	Mean	SD	Mean	SD	
VAS 1	0.13	0.344	0.09	0.288	0.30	0.470	0.124
VAS 8	0.65	0.647	0.43	0.590	0.35	0.487	0.230
VAS 16	0.87	0.757	0.96	0.638	0.91	0.733	0.897
VAS 24	0.91	0.793	1.17	0.576	1.26	0.864	0.303

GRAPH 4a : Comparison of VAS SCORES between the groups

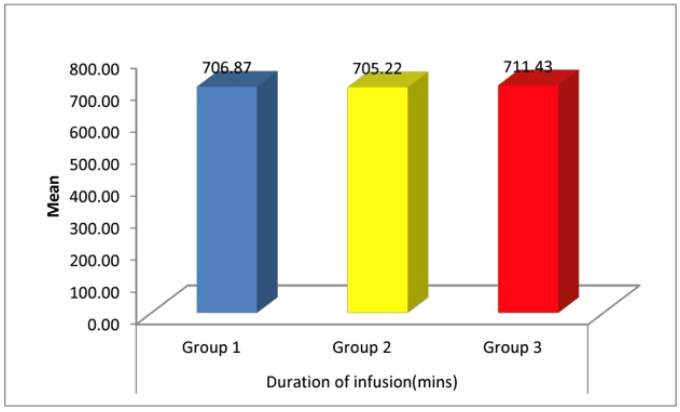


Inference: There was no significant difference in the VAS Scores between the groups.

Table 5: Duration of infusion

	Group1(n=23)		Group2(n=23)		Group3(n=23)		P
	Mean	SD	Mean	SD	Mean	SD	
Duration of infusion (mins)	706.87	8.34	705.22	8.623	711.43	10.365	0.065

GRAPH 5 : Comparison of duration of PCA infusion between the groups

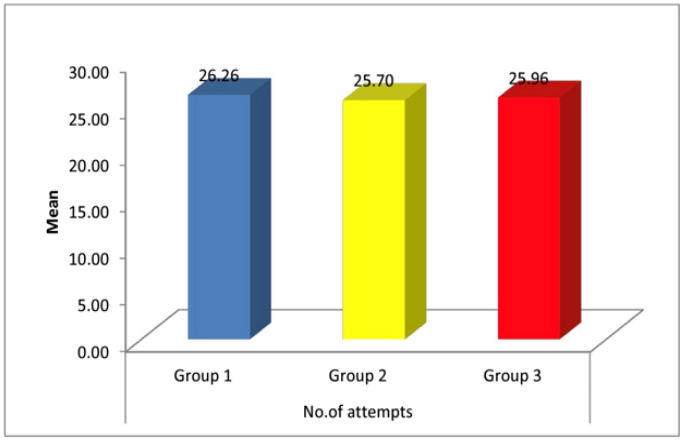


Inference: There was no significant difference in duration of infusion in between all the groups.

Table 6: Number of attempts

	Group1(n=23)		Group2(n=23)		Group3(n=23)		P
	Mean	SD	Mean	SD	Mean	SD	
Number of PCA attempts	26.26	2.435	25.70	1.490	25.96	1.364	0.579

GRAPH 6 : Comparison of number of PCA attempts between the groups



Inference: The number of PCA attempts was comparable between the three groups. The mean for Group 1 was 26.26±2.435, Group 2 was 25.70 ± 1.490 and Group 3 was 25.96±1.364.

Additional doses of analgesia requirements

Table 7.a: Comparison of additional analgesic requirement in between the group.95% CI used. For abbreviations please see text.

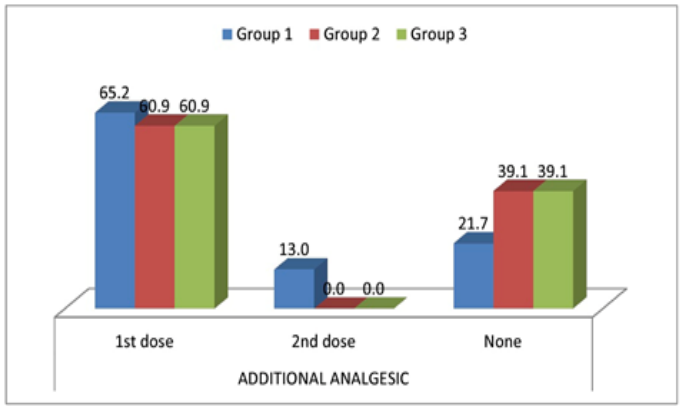
		Group1		Group2		Group3		Total	
		Count	%	Count	%	Count	%	Count	%
ADDITIONAL ANALGESIC	1st dose	15	65.2 %	14	60.9 %	14	60.9 %	43	62.3 %
	2nd dose	3	13.0 %	0	.0%	0	.0%	3	4.3%
	none	5	21.7 %	9	39.1 %	9	39.1 %	22	31.8 %
TOTAL		23	100%	23	100%	23	100%	23	100%

Fishers exact test

Table 8:

	1st hour	%	8th hour	%	16th hour	%	24th hour	%
Group1	0	0	0	0	16	69.56	3	13.04
Group2	0	0	0	0	14	60.86	0	0
Group3	0	0	0	0	14	60.86	0	0

GRAPH 8 : Comparison of additional analgesic requirement in between the groups



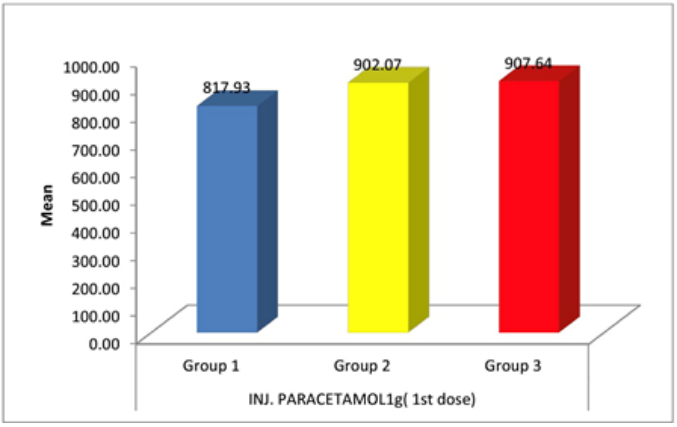
Inference: There is statistically significant difference between the groups in patients requiring additional analgesics. The number of patients requiring additional analgesic is higher in group 1.

Additional doses of analgesia requirements

TABLE 9: Comparison of 1st additional analgesic requirement in between the group.95% CI used. For abbreviations please see text.

1st additional dose of analgesia	Group 1		Group 2		Group 3		P
	number	%	number	%	number	%	
Patients requiring additional dose	15	65.21	14	60.86	14	60.86	0.044

GRAPH 10: comparison of the time to 1st additional analgesic dosage requirement between the groups



Inference: The first additional analgesic dose requirement was significantly much earlier in group 1(at 817.93 mins) when compared to group 2(at 902.07 mins) and group 3(at 907.64 mins).

Discussion

The use of neuraxial opioids has gained popularity over the last few years. They may augment the analgesia produced by local anaesthetics through direct binding with the specific spinal receptors. Opioid added to local anaesthetic for spinal anaesthesia was first introduced into clinical practice in 1979 with intrathecal morphine as a forerunner. Neuraxial administration of opioids along with local anaesthetic improves the quality of intraoperative analgesia and also provide postoperative pain relief for longer duration. Administration of fentanyl intrathecally is an established method for intraoperative anaesthesia and to supplement postoperative analgesia (Mcqually HJ et al, 1989).

A potential problem is that the patients may experience more postoperative pain if intraoperative opioids are administered due to opioid-induced hyperalgesia or acute tolerance. The outcomes measured included the postoperative pain scores for 24 hours, postoperative morphine usage, postoperative rescue analgesic usage and the adverse effects.

Conclusion

Spinal anaesthesia using local anaesthetic combined with opioid provides intraoperative analgesia along with postoperative analgesia. There was no difference in the postoperative morphine consumption and no significant difference in VAS scores among the three groups. The duration of PCA infusion was comparable among the groups. However, the time to requirement of first analgesic was significantly much earlier in group 1 when compared to other groups. Though the number of patients requiring additional analgesic were more in group 1, it was not statistically significant when comparing with the other groups.

Thus, we may attribute our observations to development of acute tolerance to opioids. But however, the clinical significance of our findings is uncertain and further studies and meta-analysis will be required.

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