

Original Articles

Comparison of Two Routes of Buprenorphine, I V vs S L, in Minor Surgeries (< 2 hrs) done under SA for Post Operative Pain Relief

KV Datir*, Indrani Hemant Kumar**, JD Borkar***

Abstract

Analgesia, haemodynamics and side effects of 3 mg/kg buprenorphine, administered by two different routes, intravenous (I V) or sublingual (S L), were compared in this study in sixty patients. These patients were undergoing minor surgery (< 2 hours duration) under spinal anaesthesia with 0.5% plain bupivacaine. The drug was administered either intravenous or sublingual, 5 min after administration of intrathecal bupivacaine. Parameters like pulse rate, respiratory rate, blood pressure, pain and sedation scores were noted at the time of administration (To), every half hourly for four hours, hourly for four hours and thereafter four hourly for 24 hours or till the patients complained pain 50% or more on the visual analogue scale, whichever was earlier.

Haemodynamic fluctuations were within acceptable limits by both routes of administration. Respiratory depression was more in intravenous than the sublingual group. Sublingual buprenorphine was superior than Intravenous buprenorphine due to high lipophilicity, suitability of administration, sweet taste, minimal side effects and long lasting effective analgesia.

Introduction

Opiates have been used since hundreds of years to reduce surgical and postoperative pain.¹⁻³ But addiction potential and respiratory depression⁴⁻⁹ have made these drugs go into disrepute. Therefore attention has been directed to opiates having mixed agonist-antagonist action, with powerful analgesic action, low addiction liability and low depressant side effects.⁴⁻⁹

Patients and Method

This was a prospective study, designed to compare postoperative analgesia and side effects with long acting opioid agonist-antagonist, buprenorphine, by two different

routes i.e. intravenous or sublingual in patients undergoing minor surgeries under spinal anaesthesia. Sixty ASA grade I or II patients, aged 18-60 yrs who gave informed consent were included in the study and observed intra-operatively as well as post-operatively in the recovery room. Patients with significant respiratory and cardiovascular abnormalities were excluded from the study. No opiate premedication was given.

Patients were divided in two groups, I V or S L, of 30 patients each.

Routine laboratory investigations i.e. Hb, PCV, S. Biochemistry, S. electrolytes, chest X-ray were done in all the patients. ECG was done in all patients over 40 yrs of age. The height and weight of patients were recorded. All of them were nil by mouth for at least 6

*Ex Lecturer, **Associate Professor, ***Ex-Professor, TNMC and BYL Nair Hospital, Mumbai.

hours prior to spinal anaesthesia.

The patients baseline pulse, respiratory rate and BP were recorded prior to anaesthesia. I V access was achieved with 18 G I V cannula and the patient was preloaded with 500 ml ringer lactate over 20 minutes. Spinal anaesthesia was given with 3 ml of plain bupivacain 0.5 % in patients with height 165 cm or less and 3.5 ml in patients whose height was more than 165 cm with 25G spinal needle. Patients were allocated randomly in either of the two groups. The IV group received I V buprenorphine 3 µg/kg and SL group received 3 µg/kg sublingually 5 min after SA. At the time of administration (T₀) PR, RR, BP, pain score and sedation score was recorded. Pain score was recorded by modified visual analogue pain scale where '0' represents no pain at all and '10' represent the worst possible pain. Sedation score by Ramsay was also recorded. The Ramsay sedation score is a six point score and is recorded as follows:

- 1 - Anxious, agitated, restless.
- 2 - Tranquil, cooperative, oriented.
- 3 - Asleep, respond to command only.
- 4 - Asleep, respond to gentle shaking
- 5 - Asleep, respond to noxious stimuli.
- 6 - Asleep not respond to any stimuli.

PR, BP (MAP), RR, Sedation and Pain score noted ½ hrly for 4 hours, hourly for next 4 hrs, 4th hourly for next 24 hrs or till the patient complains of 50% pain, when rescue analgesia was given with 3 ml of IM Diclofenac. The study was terminated after 24 hours or if the patient needed rescue analgesia, whichever was earlier. The results

were analysed using ANOVA test and Chi-Square tests.

Observation and Results

The demographic and haemodynamic variables were comparable in both the groups (Tables 1-4). The onset of analgesia was faster in the I V group compared to S L group. Peak action was achieved after 2-2 ½ hours in I V group and 2 ½ -3 hr in SL group (Table 5).

A VAS score of over 50% was achieved earlier with the IV group as compared to the SL group. None needed rescue analgesia. The maximum sedation score was same in both the groups. The duration of sedation was about 5 hours in both groups. Maximum sedation was more in IV group (statistically significant) than in SL group (Table 6). Respiratory depression requiring immediate intervention was not reported in any patient (Table 7).

Incidence of retention of urine and mild hypotension was more in IV than SL group. Vertigo, euphoria and dizziness were side effects seen in SL group.

The demographic and haemodynamic variables were comparable in both the groups (Figs. 1 & 2). The onset of analgesia was faster in the I V group compared to S L group. Peak action was achieved after 2-2 ½ hours in I V group and 2 ½ - 3 hr in SL group (Fig. 3).

A VAS score of over 50% was achieved earlier with the IV group as compared to the SL group. None needed rescue analgesia. The maximum sedation score was same in both the

Table 1 : Comparison of demographic variables between Intravenous and sublingual groups

Variables	Group				Unpaired T-Test applied		
	Intravenous		Sublingual		T-value	P-value	Difference
	Mean	SD	Mean	SD			
Age (yrs)	37.87	12.98	38.70	11.09	0.267	0.790	Not significant
Wt (kg)	54.33	9.23	57.40	7.18	1.437	0.156	Not significant
Duration of Surgery	1.29	0.31	1.33	0.34	0.514	0.609	Not significant

Table 2 : Comparison of pulse rate at various intervals between Intravenous and sublingual groups

Pulse Rate/min.	Group				Unpaired T-Test applied		
	Intravenous		Sublingual		T-value	P-value	Difference
	Mean	SD	Mean	SD			
Pre-op (T0)	81.90	10.44	80.77	9.13	-0.447	0.656	Not significant
T 1/2 hr	71.90	12.48	74.27	13.85	0.695	0.490	Not significant
T 1 hr	67.13	10.14	74.53	13.76	2.371	0.021	Significant
T 1 & 1/2 hr	67.53	9.73	71.00	13.46	1.144	0.257	Not significant
T 2 hrs	66.77	7.51	69.73	10.06	1.295	0.201	Not significant
T 2 & 1/2 hrs	65.40	7.03	68.10	9.76	1.229	0.224	Not significant
T 3 hrs	65.23	6.40	67.53	9.32	1.115	0.270	Not significant
T 3 & 1/2 hrs	65.20	5.98	67.53	8.40	1.240	0.220	Not significant
T 4 hrs	66.20	7.25	67.27	7.33	0.567	0.573	Not significant
T 5 hrs	66.28	7.38	67.41	6.81	0.610	0.544	Not significant
T 6 hrs	67.04	7.26	66.69	5.18	-0.197	0.844	Not significant
T 7 hrs	68.00	7.10	66.36	5.26	-0.837	0.408	Not significant
T 8 hrs	69.23	7.42	66.22	3.49	-1.511	0.142	Not significant
T 24 hrs	79.50	6.48	70.25	7.44	-2.652	0.019	Significant

Fall in pulse rate from baseline value started from 1/2 hr onwards in both groups. The fall in pulse rate was more pronounced and significant in the I V group than S L group ($p < 0.021$). The pulse rate was least between 3 – 4 hours in both groups. This relative fall in pulse rate persisted for 8 hrs with return to baseline pulse at 24 hrs. 6 patients in group I V and 4 patients in group S L had bradycardia (PR < 60/min). 4 patients of group I V required anticholinergic treatment. No statistically significant difference was found between the two groups on analysis of variance for pulse rate.

Table 3 : Comparison of respiratory rate at various intervals between intravenous and sublingual groups

Respiratory Rate/min.	Group				Unpaired T-Test applied		
	Intravenous		Sublingual		T-value	P-value	Difference
	Mean	SD	Mean	SD			
Pre-op (T0)	17.10	3.28	18.27	3.23	1.388	0.170	Not significant
T 1/2 hr	15.07	3.18	16.43	3.89	1.489	0.142	Not significant
T 1 hr	13.57	2.62	16.10	4.11	2.849	0.006	Significant
T 1 & 1/2 hr	12.87	2.39	15.40	3.61	3.208	0.002	Significant
T 2 hrs	12.07	1.62	14.73	3.62	3.684	0.001	Significant
T 2 & 1/2 hrs	12.13	1.96	13.93	3.04	2.726	0.008	Significant
T 3 hrs	12.03	2.21	13.47	2.73	2.239	0.029	Significant
T 3 & 1/2 hrs	12.00	2.03	13.33	2.85	2.088	0.041	Significant
T 4 hrs	12.13	2.29	13.00	2.51	1.400	0.167	Not significant
T 5 hrs	12.07	2.36	13.17	2.90	1.588	0.118	Not significant
T 6 hrs	12.28	2.70	13.23	2.54	1.297	0.201	Not significant
T 7 hrs	12.17	2.75	12.91	2.37	0.918	0.365	Not significant
T 8 hrs	12.62	2.22	12.33	1.97	-0.373	0.712	Not significant
T 24 hrs	12.75	1.83	12.25	1.28	-0.632	0.537	Not significant

There was a fall in respiratory rate in both groups by 5 breaths/min. which started from 1 hr ($p < 0.006$) with gradual progressive decrease over next 3 ½ hrs in both groups. Respiratory rate was maintained thereafter till 24 hr without significant change. Fall in respiratory rate was more in IV than S L group in the 1st 8 hrs. Three patients of I V group had RR 8/min while only 1 patient of S L group had respiratory rate < 8/min. The least respiratory rate achieved in both groups was 8/min. None needed oropharyngeal airway or IPPV treatment.

Table 4 : Comparison of blood pressure (MAP) at various intervals between intravenous and sublingual groups

Blood Pressure (MAP)-mm of Hg	Group				Unpaired T-Test applied		
	Intravenous		Sublingual		T-value	P-value	Difference
	Mean	SD	Mean	SD			
Pre-op (T0)	91.93	7.49	90.07	6.92	-1.003	0.320	Not significant
T 1/2 hr	83.37	6.66	82.07	5.50	-0.825	0.413	Not significant
T 1 hr	83.33	6.45	82.17	5.48	-0.755	0.453	Not significant
T 1 & 1/2 hr	84.00	6.35	81.97	5.49	-1.327	0.190	Not significant
T 2 hrs	85.10	6.65	83.07	4.39	-1.399	0.167	Not significant
T 2 & 1/2 hrs	85.67	7.17	83.87	6.47	-1.021	0.311	Not significant
T 3 hrs	85.70	7.27	82.97	4.11	-1.793	0.078	Not significant
T 3 & 1/2 hrs	85.87	7.54	83.83	3.86	-1.315	0.194	Not significant
T 4 hrs	86.57	7.36	83.97	3.73	-1.726	0.090	Not significant
T 5 hrs	85.86	6.65	84.00	3.79	-1.310	0.195	Not significant
T 6 hrs	86.20	7.53	83.85	3.48	-1.441	0.156	Not significant
T 7 hrs	84.61	6.92	84.32	4.64	-0.160	0.874	Not significant
T 8 hrs	85.15	7.49	84.89	4.90	-0.119	0.906	Not significant
T 24 hrs	90.38	7.67	92.63	9.74	0.513	0.616	Not significant

In both groups, there was a fall in systolic, diastolic and mean arterial blood pressures by 10-20 mmHg during the first half hour after administration of study drug and maintained in that range upto 8 hours with gradual return to baseline value by 24 hours. No significant difference was found between the groups

Table 5 : Comparison of pain score at various intervals between intravenous and sublingual groups

Pain Score	Group				Unpaired T-Test applied		
	Intravenous		Sublingual		T-value	P-value	Difference
	Mean	SD	Mean	SD			
Pre-op (T0)	0.00	0.00	0.00	0.00	Test cannot be applied		
T 1/2 hr	0.00	0.00	0.00	0.00	Test cannot be applied		
T 1 hr	0.03	0.18	0.00	0.00	-1.000	0.321	Not significant
T 1 & 1/2 hr	0.33	1.83	0.67	2.54	0.584	0.561	Not significant
T 2 hrs	2.67	5.83	1.33	3.46	-1.077	0.286	Not significant
T 2 & 1/2 hrs	4.33	7.74	4.67	6.81	0.177	0.860	Not significant
T 3 hrs	9.00	9.60	9.33	10.81	0.126	0.900	Not significant
T 3 & 1/2 hrs	15.33	10.08	14.67	12.79	-0.224	0.823	Not significant
T 4 hrs	20.67	11.43	20.33	12.73	-0.107	0.915	Not significant
T 5 hrs	28.97	11.45	27.93	10.48	-0.359	0.721	Not significant
T 6 hrs	34.40	10.44	34.23	9.45	-0.061	0.952	Not significant
T 7 hrs	35.56	10.42	32.73	11.21	-0.820	0.418	Not significant
T 8 hrs	36.15	11.93	38.89	10.23	0.685	0.499	Not significant
T 24 hrs	30.00	0.00	30.00	0.00	Test cannot be applied		

Duration of maximum analgesia was 3-8 hrs in both groups. Incidence of patients complaining 50% pain between 4-6 hrs was more in IV group than SL group. Incidence of patients complaining 50% of pain between 7-8 hours is more in SL group than in IV group. Onset of analgesia was earlier in IV group than in SL group. No statistically significant difference was found between the groups on analysis of variance for pain score.

Table 6 : Comparison of Sedation Score at various intervals between Intravenous and Sublingual groups

Sedation Score	Group				Unpaired T-Test applied		
	Intravenous		Sublingual		T-value	P-value	Difference
	Mean	SD	Mean	SD			
Pre-op (T0)	0.00	0.00	0.00	0.00	Test cannot be applied		
T 1/2 hr	0.00	0.00	0.00	0.00	Test cannot be applied		
T 1 hr	0.07	0.25	0.00	0.00	-1.439	0.155	Not significant
T 1 & 1/2 hr	0.17	0.46	0.07	0.25	-1.041	0.302	Not significant
T 2 hrs	0.53	0.63	0.37	0.67	-0.995	0.324	Not significant
T 2 & 1/2 hrs	0.77	0.82	0.67	0.96	-0.435	0.665	Not significant
T 3 hrs	0.70	0.70	0.77	0.68	0.374	0.710	Not significant
T 3 & 1/2 hrs	0.37	0.49	0.57	0.63	1.378	0.174	Not significant
T 4 hrs	0.10	0.31	0.20	0.41	1.077	0.286	Not significant
T 5 hrs	0.03	0.19	0.07	0.26	0.584	0.561	Not significant
T 6 hrs	0.00	0.00	0.00	0.00	Test cannot be applied		
T 7 hrs	0.00	0.00	0.00	0.00	Test cannot be applied		
T 8 hrs	0.00	0.00	0.00	0.00	Test cannot be applied		
T 24 hrs	0.00	0.00	0.00	0.00	Test cannot be applied		

Onset of sedation was faster (1 hr) in IV group as compared to SL group (1 1/2 hours) - ($p < 0.025$). Maximum sedation score was similar in both groups. Duration of sedation was about 5 hours in both the groups. Duration of sedation was marginally more in I V group than in SL group with no statistical significance.

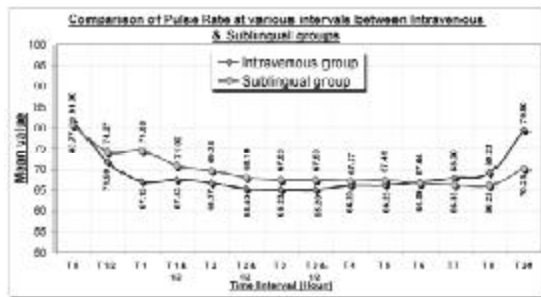


Fig. 1 : Comparison of pulse rate at various intervals between I and II groups with unpaired T-test

Fall in pulse rate from baseline value started from 1/2 hour onwards in both groups. The fall in pulse rate was more pronounced and significant in the I V group than S L group ($p < 0.021$). The pulse rate was least between 3-4 hours in both groups. This relative fall in pulse rate persisted for 8 hrs with return to baseline pulse at 24 hrs. 6 patients in group I V and 4 patients in group S L had bradycardia ($PR < 60/min$). 4 patients of group I V required anticholinergic treatment. No statistically significant difference was found between the two groups on analysis of variance for pulse rate.

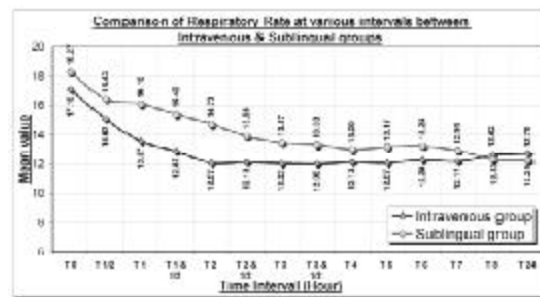


Fig. 2 : Comparison of respiratory rate at various intervals between intravenous and sublingual groups, unpaired T test

There was a fall in respiratory rate in both groups by 5 breaths/min. which started from 1 hr ($p < 0.006$) with gradual progressive decrease over next 3 1/2 hrs in both groups. Respiratory rate was maintained thereafter till 24 hr without significant change. Fall in respiratory rate was more in IV than S L group in the 1st 8 hrs. Three patients of I V group had RR 8/min while only 1 patient of S L group had respiratory rate $< 8/min$. The least respiratory rate achieved in both groups was 8/min. None needed oropharyngeal airway or IPPV treatment.

Table 7 : Side effect of Cases compared between the Groups

Side effect		Group		Total
		Intrave- nous	Sublin- gual	
Bradycardia+	No.	0	1	1
Giddiness	%	0.00%	3.30%	1.70%
Bradycardia+	No.	1	0	1
Hypotension	%	3.30%	0.00%	1.70%
Bradycardia+	No.	1	2	3
Resp.depression	%	3.30%	6.70%	5.00%
Bradycardia+	No.	2	0	2
Urine retention	%	6.70%	0.00%	3.30%
Bradycardia	No.	6	4	10
	%	20.00%	13.30%	16.70%
Euphoria	No.	0	1	1
	%	0.00%	3.30%	1.70%
Hypotension	No.	1	1	2
	%	3.30%	3.30%	3.30%
Respiratory depression	No.	3	1	4
	%	10.00%	3.30%	6.70%
Urinary retention	No.	1	2	3
	%	3.30%	6.70%	5.00%
Vertigo	No.	0	1	1
	%	0.00%	3.30%	1.70%
None	No.	15	17	32
	%	50.00%	56.70%	53.30%
Total	No.	30	30	60
	%	100.00%	100.00%	100.00%
Chi-square Test applied	Value	df	P-value	Difference is-
Pearson Chi-Square	8.192	10	0.610	Not significant
Likelihood Ratio	10.572	10	0.392	Not significant

Bradycardia and respiratory depression was found to be the predominant side effect in both groups with incidence more in IV than SL group (33% and 13% in IV group Vs 23% and 10% in SL group). Urinary retention was found in 10% patients of IV group and 3% patients of SL group. Hypotension (SBP < 90 mm Hg) was found in 6% patients of IV group 3% patients of SL group. Vertigo and euphoria was found in 3% patients of SL group were asymptomatic. There was no statistically significant difference in side effects between two groups though I V group had a marginally higher percentage of side effects.

groups. The duration of sedation was about 5 hours in both groups. Maximum sedation was more in IV group (statistically significant) than in SL group. Respiratory depression requiring immediate intervention was not reported in any patient (Figs. 3-5).

Incidence of retention of urine and mild hypotension was more in IV than SL group. Vertigo, euphoria and dizziness were side effects seen in SL group (Fig. 6).

Discussion

Buprenorphine has been studied for pre-emptive analgesia and for post operative pain relief by many authors.^{1,3,10-15} However, there are not many studies comparing I V route with S L route for post operative pain relief in indoor patients.

Buprenorphine, 3 µg/kg, has been shown to be an effective analgesic in doses used in trials. The drug has a slow onset of action with prolonged duration of analgesia.^{1,2,4,6,10,11,13-}

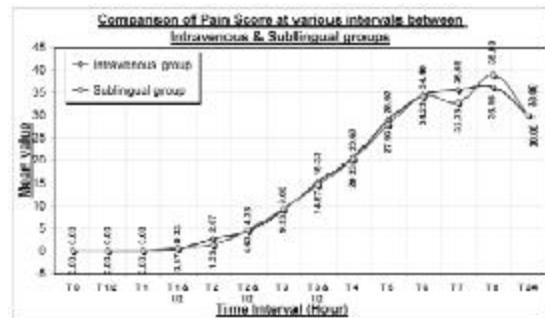


Fig. 3 : Comparison of pain score at various intervals between IV and SL groups with Chi-square test

Duration of maximum analgesia was 3-8 hrs in both groups. Incidence of patients complaining 50% pain between 4-6 hrs was more in IV group than SL group. Incidence of patients complaining 50% of pain between 7-8 hours is more in SL group than in IV group. Onset of analgesia was earlier in IV group than in SL group. No statistically significant difference was found between the groups on analysis of variance for pain score.

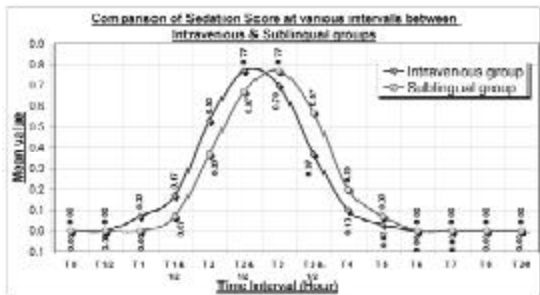


Fig. 4 : Comparison of sedation score at various intervals between IV and SL groups with Chi-square test

Onset of sedation was faster (1 hr) in IV group as compared to SL group (1 ½ hours) – ($p < 0.025$). Maximum sedation score was similar in both groups. Duration of sedation was about 5 hours in both the groups. Duration of sedation was marginally more in I V group than in SL group with no statistical significance.

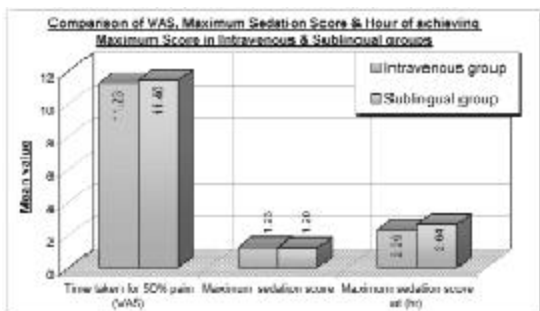


Fig. 5 : Comparison of time taken for 50% pain (VAS) maximum sedation score and time for maximum sedation score between two groups, with unpaired T-test

There was no statistically significant difference in the time taken for 50% pain complained by patient and maximum sedation score in both groups. Maximum sedation was achieved earlier in IV group (Between 2-2 ½ hr) than in SL group (between 2, ½-3 hrs) and is statistically significant ($p < 0.025$).

20

In this study, an attempt was made to compare analgesia, haemodynamic properties and side effects of buprenorphine by I V and S L routes.

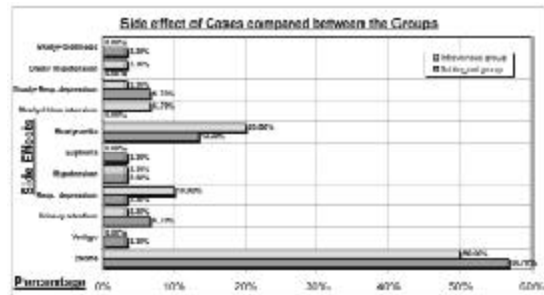


Fig. 6 : Comparison of side effect between two groups Bradycardia and respiratory depression was found to be the predominant side effect in both groups with incidence more in IV than SL group (33% and 13% in IV group Vs. 23% and 10% in SL group). Urinary retention was found in 10% patients of IV group and 3% patients of SL group. Hypotension (SBP < 90 mm Hg) was found in 6% patients of IV group 3% patients of SL group. Vertigo and euphoria was found in 3% patients of SL group were asymptomatic. There was no statistically significant difference in side effects between two groups though I V group had a marginally higher percentage of side effects.

Effectiveness of I V Buprenorphine is proven. Both routes of administration resulted in acceptable pain and sedation scores as well as acceptable fluctuation in haemodynamics. Suitability of drug by sublingual route is suggested by high lipophilicity and long duration of action with low addiction potential.^{10,13,14,17,18,20-23} Taste of the drug is sweet and route of administration is convenient for patients as well as nursing staff. Euphoria if present is an added advantage with this route.

To conclude, in indoor patients, where continuous monitoring of vitals is available, buprenorphine is a cost effective yet good analgesic with high potency, providing maximum patient comfort with minimal side effects.

References

1. Watson PJQ, McQuay HJ, Bullingham RES, Allen MC, Moore RA. Single dose comparison of Buprenorphine 0.3-0.6 mg intravenous given after operation, Clinical effects and plasma concentration. *Br J Anaesth* 1982; 54 : 37.
2. JmcQuay H, Bullingham RES, Paterson GMS, Moore RA. Clinical effect of buprenorphine during and after operation. *Br J Anaesthesia* 1980; 52 : 1013.
3. Wylie and Chuchill Davidson's Practice of Anaesthesia. Fifth edition, Lloyd-Luke (medical books)Ltd,1984, Pain and Analgesic Drugs, FJM. Reynolds, Chapter 30,802,902.
4. Ronald D Miller. Anaesthesia, Fifth edition, Churchill Livingstone 2000, Vol-1, Chapter 10, Intravenous Opioid Anaesthetics, Peter I. Bailey, Talmage D. Egan and Theodore H. Stanley (273-376).
5. Duthie DJR, Nimmo WS. Adverse effect of opioid anajgesic drugs. *Br J Anaesthesia* 1987; 59 : 61-77.
6. Robert K Stolting. Pharmacology and Physiology in AnaesthesiaPractice, Third edition. Chapter 3, Opiod agonist and antagonist, 104.
7. Tripathi KD. Essentialsof medical Pharmacology, Third edition, JAYPEE brothers medical publisher, Chapter 30, Opioid agonists antagonist, 401.
8. Goodman and Gillman's pharmacological basis of Therapeutics, Tenth edition , McGraw-Hill, Medical Publishing Division, 2001, Chapter 23, Opiod analgesics, 586,601-603.
9. Satoskar RS, Bhandarkar SD, Ainapure SS. Pharmacology and Pharmacotherapeutics, Eighteenth edition, 2003, Mumbai Popular Prakashan. Chapter 8, Opiod analgesics, Opioid antagonists, 141, 153.
10. Kathleen M Foley. The treatment of cancer pain. *The New Eng J of Medicine* 1985; 313 : 84-95.
11. Ellis R, Hains D, Shah R, Collon BR, Smith G. Pain relief after abdominal surgery- A Comparison of intramuscular morphine, sublingual buprenorphine and self administered intravenous pethidine. *Br J Anaesthesia* 1982; 54 : 421-8.
12. Simpson BRG, Parkhouse J. The Problem of Postoperative Pain. *Br J Anaesthesia* 1961 : 333-6.
13. Pedar Carl, Michel E Crawford, Neil BB Madson, Larson L. Pain relief after major abdominal surgery. A double blind controlled comparison of SL buprenorphine. IM buprenorphine and IM meperidine. *Anaesthesia-Analgesia* 1987; 66 : 147-6.
14. Shah MV, Jones DJ, Rosen M. Patent demand postoperative analgesia with buprenorphine. Comparison between sublingual and intramuscular administration. *Br J Anaesthesia* 1986; 58 : 508-11.
15. Kay B. A double blind comparison of morphine and buprenorphine in the prevention pain after operation. *Br J Anaesthesia* 1978; 50 : 605.
16. Bullingham Roy ES, McQuay HJ, Moore Andrew, Bennette MRD. Buprenorphine Kinetics. *Clinical Pharmacology Therapeutics* 1980; 28 (5) : 667-72.
17. David Brewster, Michael J. Humphrey, Michael A Mcleavy. The systemic bioavailability of buprenorphine by various routes of administration. *J Pharmac Pharmacol* 1981; 33 : 500-6.
18. Edge WG,Cooper GM, Mogan M. Analgesic effects of sublingual buprenorphine after surgery. *Anaesthesia* 1979; 34 : 463-7.
19. Fry ENS. Relief of the pain after surgery. A comparison of S.L. buprenorphine and IM papaveretum. *Anaesthesia* 1979; 34 : 549-51.
20. O'sullivan, Bullingham RES, Mcquay HJ, Poppleton P, M Ro, Molfe RA, Weir and Moore RA. A comparison of intramuscular and sublingual buprenorphine, intramuscular morphine and placebo as premedication, *Anaesthesia*, 1983; 38 : 977-84.
21. Weinberg DS. Inturrisi CE, Reidenbergh B, Moulin DE, Nip TJ, Wallenstein S, Houde RW, Foley KM. Sublingual absorption of selected opioid analgesics, *Clinical Pharamacol Therapeutic* 1988; 44 : 335-42.
22. Olley JE, Tiong GKL. Plasma level of opioid material in man following sublingual and intravenous administration of bupernorphine; exogenous/endogenous opioid interaction. *J Pharmac Pharmacol* 1988; 40 : 66-667.
23. Risbo A, Chammer Jorgrnson B, Kolby P, Pedreson J, Schamidt JF. Sublingual beprenorphine for premedication and postoperativr pain relief in orthopaedic surgery, *Acta Analgesia Scand* 1985; 29 : 180-2.