Original Article

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Comparison of Intra-Articular Bupivacaine and Neostigmine with Bupivacaine and Fentanyl for Post-Operative Analgesia in Arthroscopic Knee Surgeries

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Abstract

Background: The post-operative pain in knee arthroscopy procedures can be attributed to irritation of free nerve endings of synovial tissue, anterior fat pad, and joint capsule during surgical excision and resection1. In the recent years, new interest has focused on the cholinergic system that modulates pain perception and transmission. The present study is designed to compare the efficacy of intra- articular Bupivacaine and Neostigmine with Bupivacaine and Fentanyl for pain relief following arthroscopic surgeries. **Subjects and Methods:** Prospective, Interventional, Randomised study was conducted over 90 patients scheduled for elective arthroscopic knee surgery, who were randomly allocated into three equal groups of 30 patients each. Group I-Bupivacaine with Neostigmine, Group II-Bupivacaine with Fentanyl and Group III-Bupivacaine alone. The study drug combinations were administered Intra-articularly at the conclusion of surgery. Hemodynamic variables and Pain were observed immediately after completion of surgery (Baseline) and thereafter at fixed intervals. The duration of effective analgesia was measured from the "baseline" until the first use of rescue analgesic. The number of rescue analgesics given in 24 hours were also recorded. The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. **Results:** Requirement for first analgesia was significantly earlier in Group III (146.00±71.66 minutes) as compared to Group II (236.00±111.34 minutes) and Group I (648.00±228.55 minutes). Majority of patients of Group I (90.0%) required rescue analgesia only once while in was twice in Group II (90.00%) and thrice in Group III (86.67%). **Conclusion:** Intra-articular administration of Neostigmine in combination with Bupivacaine provided a better post-operative analgesic effect with a lower incidence of side effects and lesser requirement of rescue analgesia.

Keywords: Neostigmine, Fentanyl, Bupivacaine, Arthroscopy.

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Introduction

The post-operative pain in knee arthroscopy procedures can be attributed to irritation of free nerve endings of synovial tissue, anterior fat pad, and joint capsule during surgical excision and resection.[1] Intra-articular injection of different drugs after arthroscopy can reduce the pain significantly and decrease the need for analgesic.[2] In the recent years, new interest has focused on the cholinergic system that modulates pain perception and transmission. The acetyl-choline esterase inhibitor Neostigmine, has demonstrated a dose- dependant analgesia following spinal or epidural administration.[3,4] Moreover, in animal studies, Neostigmine when given alone through intra-articular route, has shown to bring about histo pathological changes in articular cartilage and synovium of knee joint.[5] The present study is designed to compare the efficacy of intra- articular Bupivacaine and Neostigmine with Bupivacaine and Fentanyl for pain relief following arthroscopic surgeries.

Aims and Objective

To compare the efficacy of combination of Bupivacaine and Neostigmine with Bupivacaine and Fentanyl administered intra-articularly for postoperative pain relief in patients undergoing arthroscopic knee surgeries in terms of duration of analgesia and hemodynamic changes. In addition, to note the side effects, if any, of the study drugs.

Subjects and Methods

Prospective, Interventional, Randomised study was conducted in Department of Anaesthesiology, Era's Lucknow Medical College & Hospital, Lucknow over 18 months. After obtaining approval from the Institutional Ethical Committee, 90 patients between age group 18-50 years with ASA GRADE I & II, scheduled for elective arthroscopic knee surgery were randomly allocated into three

equal groups of 30 patients each. Group I- 20 ml of 0.25% Bupivacaine + 1ml (500 µg) of Neostigmine. Group II- 20 ml of 0.25% Bupivacaine + 1 ml (50 µg) of Fentanyl. Group III- 20 ml of 0.25% Bupivacaine + 1 ml of Normal saline. The surgery was carried out under sub-arachnoid block. At the conclusion of surgery, the study drug combinations were administered by the operating surgeon into the knee joint space via 18G needle. Hemodynamic variables and Pain were observed immediately after completion of surgery (Baseline) and thereafter at 1 hour, 2 hour, 4 hours, 8 hours, 12 hours, 16 hours, 20 hours and 24 hours. The duration of effective analgesia was measured from the "baseline" until the first use of rescue analgesic. The number of rescue analgesics given in 24 hours were also recorded. Pain was assessed using 10-point Visual Analogue Scale (VAS). Time to First complain of pain with VAS score >4 in the post-operative period was recorded and Injection Diclofenac 75mg i.m was given as rescue analgesic. Adverse effects like nausea, vomiting, hypotension, bradycardia, respiratory distress, urinary retention and pruritus was documented and managed accordingly.

Statistical Tool Employed

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The values were represented in Number (%) and Mean ± SD . Analysis of Variance (ANOVA) test was used to compare the within group and between group variances amongst the study groups i.e. the three different sealers. Analysis of variance of these three sealers at a particular time interval revealed the differences amongst them. ANOVA provided "F" ratio, where a higher "F" value depicted a higher inter-group difference. Paired "t" test used to compare the change in a parameter at two different time intervals. Kruskall Wallis H Test, Mann- Whitney U test and the Wilcoxon signed rank statistic test were also used.

Results

Difference in age, gender and body weight of patients of above three groups was not found to be statistically significant. Most common diagnosis among study population was ACL tear (n=38; 42.22%) followed by Pain knee (n=33; 36.67) while less common diagnosis was PCL tear (n=14; 15.56%) and Arthritis knee (n=3; 3.33%). Difference in clinical diagnosis of patients of above three groups was not found to be statistically significant (p=0.214). Pulse rate, systolic BP and diastolic BP of patients of above three groups were found to be comparable at all the periods of observation after baseline (p > 0.05).

Table 1: Intergroup Comparison of Pain (VAS) at different time intervals

	Group I (n=30)			Group II (n=30)			Group III (n=30)			Kruskal-Wallis H test	
	Md	Mn	SD	Md	Mn	SD	Md	Mn	SD	H	P
Baseline	2.00	2.00	0.00	2.00	2.00	0.00	2.00	2.00	0.00	0.000	1.000
1 h	2.00	2.00	0.00	2.00	2.00	0.00	2.00	2.47	0.86	15.012	0.001
2 h	2.00	2.00	0.00	2.00	2.60	0.93	3.00	3.00	1.02	19.216	<0.001
4 h	2.00	2.20	0.61	4.00	3.13	1.01	2.00	2.60	0.93	14.892	0.001
8 h	2.00	2.60	0.93	2.00	2.27	0.69	2.00	2.40	0.81	2.507	0.287
12 h	2.00	2.87	1.01	2.00	2.13	0.51	4.00	3.07	1.01	15.863	<0.001
16 h	2.00	2.27	0.69	2.00	2.47	0.86	2.00	2.40	0.81	1.004	0.605
20 h	2.00	2.27	0.69	2.00	2.93	1.01	2.00	3.00	1.02	10.504	0.005
24 h	2.00	2.00	0.00	2.00	2.27	0.69	2.00	2.80	1.00	16.838	<0.001

Table 2: Intergroup Comparison of Time for first analgesia requirement (minutes) of Study Population

Group	No.	Min.	Max.	Median	Mean	S.D.
Group I	30	240	1200	720	648.00	228.55
Group II	30	120	480	240	236.00	111.34
Group III	30	60	240	120	146.00	71.66
Total	90	60	1200	240	343.33	266.52

F=92.414; p<0.001

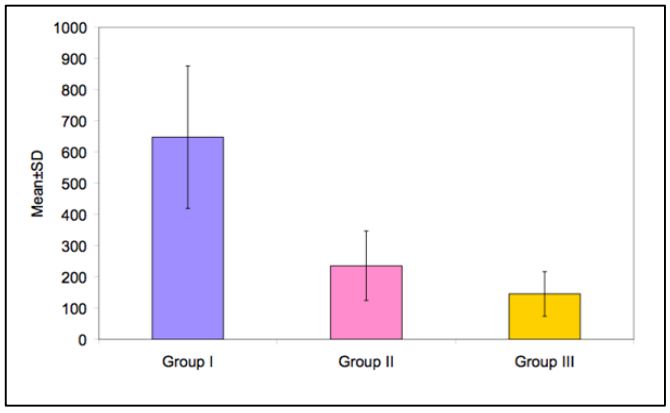

Figure 1: Intergroup comparison of time for first analgesia requirement (minutes) of study population

Table 3: Intergroup Comparison of frequency of Rescue analgesia of Study Population

No. of times rescue analgesia required	Total (N=90)	Group I (n=30)		Group II (n=30)		Group III (n=30)	
		No.	%	No.	%	No.	%
1	30	27	90.00	3	10.00	0	0.00
2	34	3	10.00	27	90.00	4	13.33
3	26	0	0.00	0	0.00	26	86.67

χ^2=128.329(df=4); p<0.001

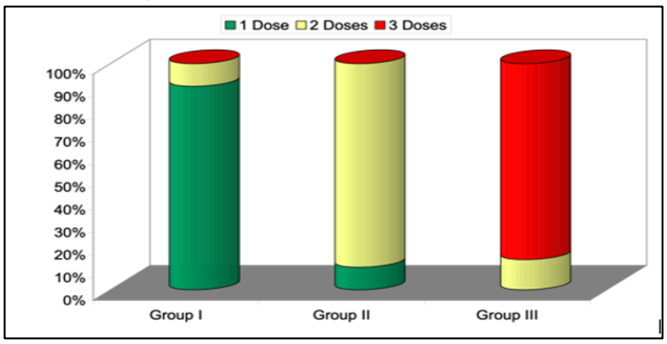

Figure 2: Intergroup comparison of frequency of rescue analgesia of study population

At baseline, pain score of patients of Group I, Group II and Group III (2.00±0.00) was found to be similar. At 1 h post operatively, pain score of patients of Group III (2.47±0.86) was found to be significantly higher as compared to Group I (2.00±0.00) and Group II (2.00±0.00). At 2 h post operatively, pain score of patients of Group III (3.00±1.02) and Group II (2.60±0.93) were found to be significantly higher as compared to Group I (2.00±0.00). At 4 h post operatively, pain score of patients of Group II (3.13±1.01) and Group III (2.60±0.93) were found to be significantly higher as compared to Group I (2.20±0.61). [Table 1]

Requirement for first analgesia was significantly earlier in patients of Group III (146.00±71.66 minutes) as compared to Group II (236.00±111.34 minutes) and Group I (648.00±228.55 minutes). Between Group difference Mean ± SD among Group II & Group III was not found to be statistically significant. Order of requirement of rescue analgesia was Group III ≈ Group II < Group I. [Table 2]

Majority of patients of Group I (90.0%) required rescue analgesia only once while majority of patients of Group II (90.00%) required rescue analgesia two times and majority of patients of Group III (86.67%) required rescue analgesia three times during the period of observation. None of the patients of Group I and Group II required rescue analgesia for three times and none of the patients of Group III required rescue analgesia for one time only. Difference in number of times requirement of rescue analgesia among patients of above three groups was found to be statistically significant.

Table 4: Intergroup Comparison of Adverse effects in Study Population

Adverse effects	Total (N=90)	Group I (n=30)		Group II (n=30)		Group III (n=30)		Statistical significance	
		No.	%	No.	%	No.	%	χ^2	P
Nausea	20	0	0.00	8	26.67	12	40.00	14.400	0.001
Vomiting	13	0	0.00	6	20.00	7	23.33	7.732	0.021

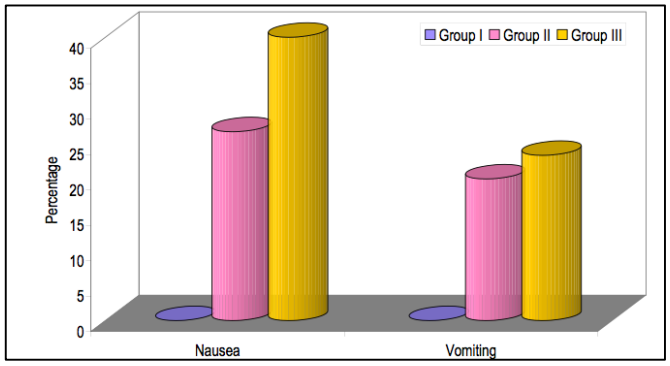

Figure 3: Intergroup comparison of adverse effects in study population

Adverse effects Nausea and vomiting were observed in higher proportion of patients of Group II and Group III as compared to Group I. Difference in prevalence of patients with adverse effect of Nausea among patients of Group I (0.0%), Group II (26.67%) and Group III (40.00%) was found to be statistically significant (p<0.001). Similarly, prevalence of patients with adverse effect of Vomiting among patients of Group I (0.0%), Group II (20.00%) and Group III (23.33%) was also found to be statistically significant.

Discussion

Intra-articular injection of different drugs after arthroscopy can reduce the pain significantly and decrease the need for analgesic.[6] Intra articular injection of neostigmine acts by stimulation of peripheral muscarinic receptors, and hence does not accompany the side effects related with use of opioids that act by stimulation of nicotinic receptors and hence is often considered to be relatively safer.[7] It has been shown to be effective when used singly after the arthroscopic knee surgery or when given in combination with Bupivacaine.[7-12] Despite its potential to reduce the opioid related side effects, there are no comparative studies available comparing its efficacy in combination with Bupivacaine to that of Fentanyl (an opioid) in combination with Bupivacaine.

Age of patients ranged from 18 to 50 years with a mean age 32.47 years. Statistically, there was no significant difference among groups with respect to age. An attempt was made not to include elderly patients in the study as the pharmacodynamics of Neostigmine has been shown to be affected by age.[13,14] In different previous studies too, inclusion of elderly has been avoided, probably for this reason7. In their study, Datta and Madhusudanan[9] restricted the age range from 22 to 35 years only. Yang et al.[7] too in their study included patients up to 60 years of age and reported the mean age of patients between 37 to 44 years in different groups.

During the entire course of study, the three study groups did not show a significant difference in hemodynamic parameters like heart rate, systolic blood pressure, diastolic blood pressure. Moreover, no adverse events like hypotension, hypertension, bradycardia, tachycardia and respiratory depression took place, thus showing that both the drug combinations were safe and did not pose any cardiovascular risk. This hemodynamic profile is similar to various studies reviewed by us that have not reported any serious hemodynamic event in Fentanyl or Neostigmine group.[9-12,15-22] Kayacan et al.[8] compared intra- articular Neostigmine to intra-articular Tramadol, Tenoxicam and Bupivacaine and found that compared to Bupivacaine group, Neostigmine had a relatively much stable hemodynamic profile, thus indicating that Neostigmine exercises a better hemodynamic control as compared to Bupivacaine. In the present study, Bupivacaine was used in all the three groups, however, hemodynamic profile of Neostigmine was no different from Bupivacaine alone group thus signifying that Neostigmine did not induce any additional hemodynamic change and thus was safe to be used even when used in combination with Bupivacaine.

In present study, all the cases in three groups had pain score of 2 at baseline. However, at 1 hr, both the study groups maintained the mean pain score to 2 whereas in control group the mean VAS score for pain was significantly higher (2.47±0.96). However, by 4 hr Fentanyl group had maximum pain scores. At 8 and 12 hours intervals, mean pain scores

were higher in Neostigmine group as compared to that in Fentanyl group. However, the pain scores must be interpreted in context with the time taken for rescue analgesia. In Neostigmine group, the mean time taken for rescue analgesic was 648±228.55 minutes (minimum 240 min, maximum 1200 min) whereas in Fentanyl group this duration was 236±111.34 min (minimum 120 min, maximum 480 min). However, in Bupivacaine alone group this duration was only 146±71.66 min (minimum 60 and maximum 240 hours). The median period was 720 min, 240 min and 120 min in Neostigmine, Fentanyl and Bupivacaine groups respectively. This implies that in Bupivacaine group, almost half the patients had received their first rescue analgesic dose within 120 min. Thus after 120 minutes interval, the pain scores in Bupivacaine group were influenced by the rescue analgesic. Similarly, in Fentanyl group, at least half the patients had received rescue analgesic by 240 min. Hence, in Fentanyl group the pain scores were substantially affected at 240 min and thereafter with the introduction of rescue analgesia. In contrast, in Neostigmine group, none of the patients required analgesia by 240 min and the proportion of patients requiring analgesia reached to 50% or above at only 720 minutes. Thus, the pain scores in Neostigmine group remained free from rescue analgesic effect up to 720 minutes.

The findings in present study are similar to the observations made by Yang et al.[7] who observed that 500 µg of intra-articular Neostigmine as compared to 2 mg intra-articular Morphine and intra-articular Normal saline was able to not only prolong the rescue analgesic free period but also had significantly lower VAS scores at all time periods up to 24 hr. In their study, mean rescue analgesia free duration was close to 50 min in Normal saline, close to 200 min in Morphine and close to 350 min in Neostigmine group. Relatively higher rescue analgesic free time in present study could be attributable to the additional use of 0.25% Bupivacaine. In another study, Lee12 showed that even Neostigmine alone provides a comparable response as compared to addition of 0.125% Bupivacaine, thus showing that Neostigmine is a useful and strong analgesic when administered intra-articularly among patients undergoing arthroscopic knee surgeries.

Datta and Madhusudanan,[9] in their study among patients undergoing arthroscopic knee surgery also reported that as compared to Bupivacaine alone group, Neostigmine in combination with Bupivacaine increased the post- operative rescue analgesic free time by more than twice. In their study, they made comparison of these two modalities with Morphine alone group and found that Morphine alone group had rescue analgesic free time lesser than half, thus showing that opioids alone had even poorer post-operative analgesic effect as compared to Bupivacaine alone group, whereas Neostigmine alone group performed similar to Neostigmine in combination with Bupivacaine. Thus signifying that intra-articular administration of Neostigmine either alone or in combination with Bupivacaine has superior analgesic effect as compared to either Bupivacaine alone, opioids alone or a combination of Bupivacaine & opioids.

A more objective assessment of rescue analgesic free time was done by Algaol et al.[10] in a study that compared intra-articular 500 µg Neostigmine to 2 mg Morphine and 100 mg Bupivacaine and showed the mean rescue analgesia free time in the three groups to be 517.2 min, 300.6 min and 308 min respectively. Thus, as compared to opioid group, Neostigmine group had 1.72 times longer analgesic free time and as compared to Bupivacaine group it had 1.68 times longer analgesic free time. In present study when used in combination with Bupivacaine, Neostigmine had 4.44 times longer analgesic free time as compared to Bupivacaine alone and 2.75 times longer analgesic free time as compared to opioid + Bupivacaine group. The higher efficacy against Bupivacaine alone group in present study could be attributable to the addition of Bupivacaine with Neostigmine instead of Neostigmine alone as in their study. Kayacan et al.[8] in their study did not find a significant difference in rescue analgesia free time between Neostigmine alone and Bupivacaine groups, however, this may be owing to a higher concentration of Bupivacaine used in their study (0.5%) which was twice that used in present study (0.25%), against the same dosage of Neostigmine as used in present study (500 µg).

Unfortunately, there are no studies available comparing Neostigmine with Fentanyl either alone or in combination with Bupivacaine. Most of the neighbouring evidence comes from the studies that have compared Morphine with Neostigmine and found that Neostigmine outperforms the Morphine. Given the fact that Fentanyl has a lesser analgesic effect as compared to Morphine, Neostigmine out performed Fentanyl too.[9,10]

In present study, the number of rescue dosages showed an incremental trend with 90% of those in Neostigmine group requiring only single dose of rescue analgesic while 90% of those in Fentanyl group required only two dosages of rescue analgesic but 86.67% of those in Bupivacaine alone group required 3 rescue dosages of analgesia. This finding indirectly indicates the total amount of rescue analgesia to be almost three times that of Neostigmine in Bupivacaine and almost 2 times higher than that of Neostigmine in Fentanyl group. Similar to results of present study, Algaol et al.[10] in their study showed consumption of rescue analgesic up-to 72 hours to be 2.3 times higher in both Morphine as well as Bupivacaine groups. Mitra et al.[18] in their study made observations up-to 8 hrs and found that number of patients requiring analgesia was 2.4 times Fentanyl combination. Prolongation of analgesic effect up-to 1200 minutes (20 hrs) is in itself an indicator of lesser analgesic requirement in Neostigmine group as compared to Fentanyl and Bupivacaine groups in present study.

On evaluation of side effect profile of present study, we did not find any CNS side effect such as nausea and vomiting in Neostigmine supplemented group. This could be probably due to a nicotinic receptor sparing action of Neostigmine, when given intra articular. However, a high prevalence of patients in Bupivacaine alone group presenting with complaints of nausea and, vomiting in Bupivacaine and Fentanyl group remains an issue. One of the reasons for higher proportion of these side effects in patients could be owing to a higher use of rescue analgesia in these groups.

These outcomes are useful in providing a better patient satisfaction, early mobilization and lesser discomfort to the patients. Incidentally, this is the first study that has compared intra-articular Fentanyl and Bupivacaine combination with

Neostigmine and Bupivacaine combination in arthroscopic knee surgeries and was found to be in accordance with neighbouring evidence available. However, these findings still need further exploration for different drug-dose combinations and considering the efficacy of Neostigmine alone to be as beneficial in certain studies, further studies are recommended on different drug-dose combinations. Moreover, studies incorporating hospital stay, patient higher in Bupivacaine alone group as compared to Bupivacaine-satisfaction and financial implications as outcomes are also recommended to assess the impact of different interventions in more objective terms.

Conclusion

The findings of present study suggest that Neostigmine in combination with Bupivacaine provided a better post-operative analgesic effect with a lower incidence of side effects and lesser requirement of rescue analgesia. On the basis of observations made in our study in terms of efficacy and adverse effects of the study drug combinations, intra-articular administration of combination of Bupivacaine and Neostigmine can effectively and safely be recommended for post-operative pain relief in patients undergoing arthroscopic knee surgeries. Though the results of the present study are logical and explainable, further substantiation and validation of outcomes of the study is recommended.

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