Evaluation Of The Efficacy And Safety Of Butorphanol Nasal Spray In The Management Of Postoperative Pain

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Citation

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Abstract

Objective: To evaluate the efficacy and safety of Butorphanol nasal spray in the management of postoperative pain in patients with orthopedic surgery.

Materials and Methods: This prospective, open and non-comparative study was conducted on outpatient basis by qualified investigators at three different centers. A total of 105 patients with postoperative pain were enrolled in the study. The enrollment of the patients was as per inclusion/exclusion criteria. After obtaining informed consent they were individually interviewed, examined, investigated and treated as per study protocol. The treatment included one dose of Butorphanol nasal spray in each nostril equivalent to 2 mg of Butorphanol for the period of 24 hours. They were followed up at the end of 1 hour, 2, 4, 6, 12 and 24 hours. They were asked to avoid any other concomitant medication without the knowledge of the treating physician.

Results: A significant improvement in the pain score of the patients was observed at the end of 15 min. The treatment with Butorphanol nasal spray is associated with very few adverse events. Tolerability of the treatment was also reported to be excellent in the majority of the study population. Nasal administration with faster absorption offers advantages of rapid onset and patient control with relative ease of administration. It bypasses gastrointestinal and hepatic presystemic elimination and is also applicable in patients with nausea and vomiting.

Conclusion: The present study concludes that Butorphanol nasal spray is highly effective, safe and well tolerable in postoperative pain management and seems to be a good alternative to both oral and injectable Butorphanol treatment.

INTRODUCTION

Pain is as old as human being and is becoming more and more troublesome to mankind with greater incidences of medical surgeries. Many surgical procedures are associated with extreme painful conditions which are associated with physical, psychological and immunological depression. The field of postoperative pain management is being given more and more attention as it is an essential component of the care of surgical patients. Inadequate pain control, apart from being inhumane, may result in increased morbidity or mortality. The overriding principle of postoperative pain management is to provide a general background of analgesia that is sufficient to permit normal activities, along with additional analgesic supplements to cover any painful activity (dynamic pain). Breaking the pain cycle at an early stage may prevent central sensitization and, consequently, chronic pain. A second objective is to improve surgical outcome with the goals of enabling early ambulation and recovery of gastrointestinal function which in turn reduce cardiopulmonary morbidity, psychological stress, anxiety and insomnia; and preventing a poor learned response to future pain episodes.

A wide area of postoperative pain management is covered by afferent neural blockade with local anesthetics. Next in order of effectiveness are high dose opioids, epidural opioids and clonidine, patient controlled opioid therapy and Non-Steroidal Anti-Inflammatory Agents.

Butorphanol is a synthetic opioid derivative possessing agonist-antagonist activity at opioid μ_2-receptors and additional agonist activity at opioid -receptors. The analgesic efficacy of Butorphanol is comparable with that of Morphine, Mepiridine, and other opioids. However, the safety concerns with Butorphanol are much lower compared to other opioids, especially the addiction potential. The 14 years of safe and effective use of Butorphanol injection

make Butorphanol the 'drug of choice' in a number of painful conditions.

In recent years, nasal drug delivery systems emerged as a suitable alternative for the common route of intravenous and oral dosing. Nasal administration may offer advantages such as ease of administration, rapid onset and patient control. It bypasses gastrointestinal and hepatic presystemic elimination and is applicable in patients with nausea and vomiting. Nasal drug delivery provides prompt onset of action which is one of the primary objectives in treating acute pain episodes. Butorphanol nasal spray is formulated with the aim of better patient acceptance without compromising its therapeutic efficacy.

MATERIALS AND METHODS

This prospective, open, non-comparative study was conducted on outpatient basis by qualified physicians (investigators) at three different centers. A total of 105 patients suffering from postoperative pain were enrolled in the study at the three centers. The patients with postoperative pain were educated about the purpose and nature of the study by the investigators. The enrollment of patients in the study was in accordance to patient's willingness and inclusion and exclusion criteria. The signed informed consent was obtained from every patient before their inclusion in the study.

The inclusion criteria for patient enrollment included a) patient of either sex 18 years and above, b) patient undergoing orthopedic surgery on upper or lower extremity with pain in postoperative period within 24 hours and c) patient ready to give informed consent. The patients were excluded from the study if a) patients required general anesthesia, b) patients had received any analgesics, over-the-counter medication or centrally acting drugs within 4 hours of the study, c) patients had alcoholism or drug abuse within one year of the study, d) patients were mentally retarded, e) patients were suffering from any physiological or pathological condition which may alter the results of the study and f) patients had participated in a medical, surgical or pharmaceutical investigation at the time of the study in which an investigational new drug was dispensed to the patient within the last six months. The study patients were screened for their demographic profiles which included age, sex and weight. The patients were also subjected to normal biochemical and hematological testing.

Each patient was administered one dose of Butorphanol nasal spray in each nostril, equivalent to a total dose of 2 mg of Butorphanol for a period of 24 hours. The patients were followed up at the end of 1 hour, 2, 4, 8, 12 and 24 hours. All the patients were asked not to take any other medication without permission of the treating physician.

The efficacy and tolerability of Butorphanol nasal spray was evaluated by using parameters like pain intensity, pain relief and pain half gone. The score for each parameter is given in Table I.

Figure 5

Figure 1: Changes in mean score of pain intensity

Evaluating Parameters	Score			
	0	1	2	3
Pain Intensity	None	Slight	Moderate	Severe
Pain Relief	None	Slight	Moderate	Severe
Pain half gone	---	Yes	No	---

In addition to patients' response, investigators' opinions were also recorded. Global efficacy and tolerability of Butorphanol nasal spray was judged on a four point scale by the investigators as excellent, good, fair and poor.

As reporting and records of adverse events are of utmost importance, the study population was under observation during the study period for any adverse event. In addition to the monitoring records, patients were asked to keep a record and report on their own, on any unwanted effect experienced during the study period.

The data from different centers was pooled and collected data was tabulated and analyzed using an appropriate test of significance (ANOVA Krushkal Walli's test).

RESULTS

A total of 105 patients suffering from postoperative pain were screened before and during the study in three centers.

DEMOGRAPHIC PROFILES

The demographic profiles of the patients enrolled in the study as per inclusion-exclusion criteria are shown in Table II. The enrolled patients were in the age group of 19 to 62 years with a mean age of 40.85 (±13.88); 66.7 % of the enrolled patients were males. The weight of the enrolled patients ranged from 40 to 86kg with a mean of 60.11(±11.94).

Figure 2

Table 2: Demographical characteristics of the study population

Parameter		Values
Age (Yrs)	Mean	40.85
	S.D.	13.88
	Range	19-62
Weight (Kg)	Mean	60.11
	S.D.	11.94
	Range	40-86
Sex (%)	Male	70(66.7)
	Female	35(33.3)

PHYSICAL EXAMINATION

Table III reveals that all the examinations like pulse rate, blood pressure and respiratory rate were within normal limits at baseline.

Figure 3

Table 3: Profile of physical examination

Examination	Mean ±SD
Pulse rate Min^{-1}	79.82 ±6.70
Systolic blood pressure mm/Hg	120.19 ±13.04
Diastolic blood pressure mm/Hg	79.65 ±7.05
Respiratory rate Min^{-1}	16.67 ±3.35

OBJECTIVE EFFICACY PARAMETERS

The reduction in pain intensity was rated by the patients and is shown in table IV. A statistically significant fall in the pain score was observed by the end of 15 min till the end of treatment (Figure I). The basal score of pain intensity was 70.06 ± 10.60 which came down to 19.19 ± 3.71 by the end of 24 hours, indicating a statistically significant decrease in postoperative pain stimuli.

Figure 4

Table 4: Changes in mean score of pain intensity after the treatment

Duration in hours	Mean score (Mean±SD)
Basal	70.06 ±10.60
15 min.	*59.17 ±9.11
30 min.	*46.45 ±8.60
1	*40.34 ±8.68
2	*37.33 ±9.89
4	*30.59 ±7.98
6	*28.47 ±7.48
12	*25.35 ±6.36
24	*19.19 ±3.71

ANOVA Kruskal Walli's Test: *P<0.05 (significant)

Figure 6

Table 5: Overall global efficacy of treatment by investigators

Assessment	No. of Cases	Percentage
Excellent	11	10.5
Good	78	74.3
Fair	12	11.4
Poor	04	03.8
Total	105	100.0

Overall assessment of efficacy as rated by the investigators:

Table V shows the ratings on overall efficacy by the investigators. Investigators categorized 84.8% of patients as showing either excellent or good improvement, while only 15.2% of patients fell in the fair and poor category. (Figure II)

Figure 7

Figure 2: Overall Global efficacy of treatment

Figure 8

Table 6: Overall global tolerability of treatment by investigators

Assessment	No. of Cases	Percentage
Excellent	76	72.4
Good	16	15.2
Fair	08	07.6
Poor	05	04.8
Total	105	100.0

SAFETY AND TOLERABILITY

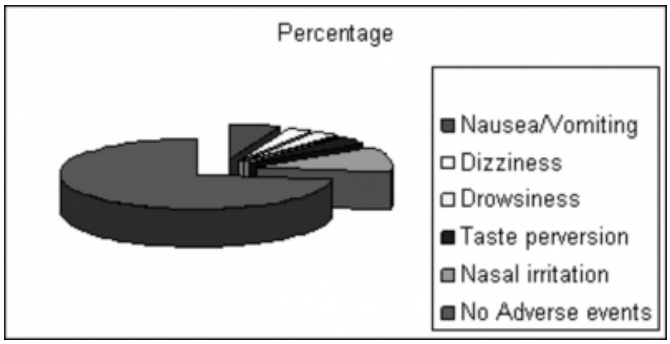
The Butorphanol treatment was observed to be safe and tolerable as 87.6% of the total study patients had an excellent to good tolerance to the treatment and 12.4% showed fair or poor tolerance (Table VI, figure III). Not a single patient was withdrawn due to safety and tolerability concerns.

Figure 9

Figure 3: Overall Global tolerability of Treatment

Figure 10

Figure 4: Frequency of adverse events



ADVERSE EVENTS

Out of 105 patients who completed the study, only 22 patients complained of some minor problems like nasal irritation, nausea/vomiting, drowsiness, taste perversion and dizziness. None of the patients experienced serious adverse events during the study period. Adverse events observed and reported over the study period are listed in table VII.

Figure 11

Table 7: Profile of adverse events

Adverse events	No. of cases (N= 105)	Percentage
Nausea/Vomiting	07	06.7
Dizziness	03	02.9
Drowsiness	04	03.8
Taste perversion	04	03.8
Nasal irritation	13	12.4
Hypotension	--	--
Others	--	--
Total	22	20.9

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DISCUSSION

In the present study, an attempt was made to evaluate the efficacy and safety of Butorphanol nasal spray in the management of postoperative pain. The results of the study demonstrate that Butorphanol nasal spray is highly effective in the treatment of postoperative pain and is very safe and well tolerated by the patients. A significant improvement in the pain score of patient was observed by the end of 15 minutes till the completion of study. The treatment with Butorphanol nasal spray is associated with very few adverse events. Further, there were no alterations in hematological and biochemical parameters with Butorphanol nasal administration. The tolerability of Butorphanol nasal spray was reported to be excellent or good in the majority of the study population by the investigators.

CONCLUSION

The present study concludes that Butorphanol nasal spray is highly effective in postoperative pain management and seems to be a good alternative to injectable Butorphanol treatment. It is also demonstrated that Butorphanol is safe by nasal drug delivery and is well tolerated by the patients.

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