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To Deduce Optimal Fentanyl Infusion Dose for Effective Analgesia with Minimal Side Effects and Maximum Hemodynamic Stability

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ABSTRACT

Objective: To deduce optimal fentanyl infusion dose for effective analgesia with minimal side effects and maximum hemodynamic stability. **Material and methods:** In our prospective study, we compared three groups (of 30 patients each) namely group 2, 3, 4 receiving three different doses of fentanyl (20 μg, 30 μg, 40 μg), respectively with control group (Group 1) receiving conventional analgesics through intramuscular or intravenous route. Effective analgesia was rated on linear visual analog scale (VAS) with minimum side effects and most stable hemodynamic parameters. **Results:** The VAS scores, at rest, were significantly lower for epidural fentanyl groups as compared to control group. Mean blood pressure and pulse rate in all groups were comparable at all times. The incidence of side effects was similar in the three fentanyl groups as compared to control group. **Conclusion:** Fentanyl dose of 40 μg is the optimal epidural dose of background infusion along with patient on demand analgesia in terms of maximum analgesic efficacy, maximum hemodynamic stability and minimum side effects in patients undergoing unilateral total knee replacement.

Keywords: Fentanyl infusion, analgesia, optimal dose, unilateral total knee replacement

"The greatest evil is physical pain" —Saint Augustine

Adequate relief of postoperative pain is the cornerstone of any acute pain management service in the modern era. Introduction of new pain management standards by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and recognition of the untoward consequences of uncontrolled postoperative pain have led to a greater appreciation for the importance of acute postoperative pain control. Inadequate control of postoperative pain may result in a higher incidence of chronic postsurgical pain, increased postoperative morbidities and worsened patient-oriented outcomes such as quality of life.

In the past, postoperative pain experienced by patients was treated conventionally with boluses of intramuscular or intravenous analgesics either on demand or at fixed intervals, which provided inadequate analgesia for inappropriate length of time. These two routes are least desirable because while intramuscular route is painful, both routes produce unpredictable blood levels due to erratic absorption. Patient dissatisfaction is common because of delays in drug administration and incorrect dosing. Cycles of sedation, analgesia and inadequate analgesia are common.

After knee surgery, poorly managed pain may inhibit the early ability to mobilize the knee joint. This, in turn, may result in adhesions, capsular contracture and muscle atrophy, all of which may delay or permanently impair the ultimate functional outcome, increased complications and diminished patient oriented outcomes such as quality of life and satisfaction. Early mobilization results in shorter hospital stay and cost containment and better resource utilization.

Postoperative epidural analgesia has been used in orthopedic surgeries and reported to expedite the achievements in postoperative rehabilitative milestones, reduce postoperative morbidity and decrease the length of hospital stay, compared with general anesthesia.

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Since there is lack of availability of sufficient data on "dose response" studies done with epidural fentanyl and a lack of consensus on its efficacy as compared to the traditional analgesic modalities, we planned this study to compare the analgesic effects of various doses of epidural fentanyl (background infusion) along with "on demand" boluses to determine the "optimal dose" postoperatively in patients undergoing unilateral total knee replacement.

MATERIAL AND METHODS

After obtaining informed consent from each and every patient, 120 (American Society of Anesthesiologists [ASA] physical status I or II) patients of either sex, scheduled for elective unilateral knee replacement were enrolled in the study. Their age ranged from 20 to 70 years.

Adult patients who were to undergo unilateral total knee replacement under spinal anesthesia were divided randomly into four groups of 30 patients each for the purpose of this study. Patients were randomly assigned to one of the four groups to receive either none (Group 1 receiving traditional intravenous or intramuscular analgesics referred to as "control" group) or 20 μg/hr (Group 2), 30 μg/hr (Group 3), 40 μg/hr (Group 4) dose of background epidural fentanyl infusion along with "on demand" dose of 20 μg fentanyl.

Combined spinal epidural set: The combined spinal epidural set consisted of -

- Sponge holding forceps
- Sterile gauze pieces
- Sterile towel
- Glass syringe (10 and 20 mL)
- Epidural Kit
- Spinal needle 26G
- Sterile dressing.

Visual Analog Scale

The linear visual analog scale (VAS) was used to assess the pain and pain relief of the patients. It consists of a straight line with 0.5 cm segments. One end having a mark 'O' represented "no pain" and the other having mark '10' represented "worst imaginable pain".

Interpretation of the VAS was explained to each and every patient during pre-anesthetic check-up and was explained for the second time after surgery in the recovery room before starting the background infusion of fentanyl. It was thus ascertained that every patient is able to aptly correlate his pain and accurately report it when asked about the same. The surgery was performed under spinal anesthesia. In the postoperative recovery room, before starting the individual background infusion, return of active toe movements was confirmed.

Any "breakthrough pain" before the return of active toe movements was treated likewise with epidural bolus dose of 20 μg but the background infusion was started only after the return of active toe movements and on confirmation of catheter position. Patients experiencing severe breakthrough pain and requiring analgesia even after loading epidural dose of 20 μg fentanyl, before return of active toe movements were excluded from the study. All patients were monitored before starting infusion (0 hour) and for up to 36 hours at 4 hours, 8 hours, 12 hours, 24 hours and 36 hours, respectively after starting epidural fentanyl infusion.

Blood pressure, pulse rate, respiratory rate, SpO_2, pain (as per sedation score), nausea/vomiting (as per nausea, vomiting score), adverse effects (e.g., pruritus, skin allergy, urinary retention respiratory depression) - noted and treated with naloxone/ondansetron. The Duncan's mean test was used to compare the four groups for demographic variables, hemodynamic parameters, VAS scores, analgesia quality, received demand doses and quantifying side effects each time of the study i.e., at 0, 4, 8, 12, 24, 36 hours, respectively. The data were compiled and analyzed to compare the analgesic efficacy of various doses of epidural fentanyl and to determine the optimal dose in terms of effective pain control, minimal number of additional demands made by patient, minimum sedation, maximum hemodynamic stability and minimum side effects.

OBSERVATION AND RESULTS

Hemodynamic parameters were in normal range during entire perioperative period and there was no serious concern.

The mean VAS in Group 1 was 3.62 ± 0.39, in Group 2 was 2.48 ± 0.34, in Group 3 was 1.42 ± 0.31 and in Group 4 was 0.97 ± 0.27. The difference of mean VAS was statistically significant in Group 1 vs. 2, Group 1 vs. 3, Group 1 vs. 4 (Table 1).

The analgesic efficacy in the four groups of patients at 0, 4, 8, 12, 24, 36 hours has been defined as (i) Excellent if mean VAS was between 0 and 3; (ii) Good if mean VAS was between 4 and 6 and (iii) Poor if mean VAS was between 7 and 10. This shows that there was significant reduction in pain score (VAS) as the background infusion dose of fentanyl increased from 20 μg/hr in Group 2 to 40 μg/hr in Group 4 (Table 2).

Table 1. VAS Score in the Groups 1 to 4

G-1 (n = 30)		G-2 (n = 30)		G-3 (n = 30)		G-4 (n = 30)		Significant pairs	F value
Mean	SD	Mean	SD	Mean	SD	Mean	SD		370.80
3.62	0.39	2.48	0.34	1.42	0.31	0.97	0.27	G-2 vs. G-1 G-3 vs. G-1 G-4 vs. G-1 G-3 vs. G-2 G-4 vs. G-2 G-4 vs. G-3	

Table 2. Analgesic Efficacy in the Four Groups of Patients at 0, 4, 8, 12, 24, 36 Hours

VAS Group	G-1 (n = 30)		G-2 (n = 30)		G-3 (n = 30)		G-4 (n = 30)		Significant pairs	F value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
VAS0	2.10	0.60	1.83	0.38	1.80	0.61	1.86	0.62	-	1.73
VAS4	4.43	1.04	3.03	0.85	1.33	0.60	0.97	0.61	G-4 vs. G-1 G-4 vs. G-1 G-3 vs. G-2 G-3 vs. G-1 G-2 vs. G-1	121.08
VAS8	4.13	1.19	2.73	0.64	1.37	0.61	0.97	0.56	G-4 vs. G-2 G-4 vs. G-1 G-3 vs. G-2 G-3 vs. G-1 G-2 vs. G-1	98.12
VAS12	4.23	0.81	2.80	0.76	1.46	0.73	0.80	0.66	G-4 vs. G-3 G-4 vs. G-2 G-4 vs. G-1 G-3 vs. G-2 G-3 vs. G-1	124.75
VAS24	3.60	0.72	2.33	0.54	1.37	0.67	0.60	0.56	G-4 vs. G-3 G-4 vs. G-2 G-4 vs. G-1 G-3 vs. G-2 G-3 vs. G-1 G-2 vs. G-1	126.74
VAS36	3.23	0.81	2.17	0.46	1.20	0.96	0.63	0.67	G-4 vs. G-3 G-4 vs. G-2 G-4 vs. G-1 G-3 vs. G-2 G-3 vs. G-1 G-2 vs. G-1	69.45

DISCUSSION

Postoperative pain is the most common form of pain encountered by the anesthesiologist. The associated morbidity and severity requires adequate management of postoperative pain. Besides the humanitarian cause, the effective management of postoperative pain is mandatory also for prevention of complications like nausea and vomiting, negative nitrogen balance, deep vein thrombosis, lung atelectasis and other respiratory complications. Ureteral and bladder hypomobility, which may delay recovery and prolong hospitalization.

When an opioid is administered to the chief site of action, the substantia gelatinosa of the dorsal horn, it produces a highly selective depressing action on nociceptive pathway in the rexed laminae of the dorsal horn without effecting motor sympathetic or proprioceptive pathways thus allowing pain relief without sympathetic or motor blockade.

The cardiovascular and hemodynamic effects of fentanyl have usually been relatively small and limited to minimal depression in the heart rate, blood pressure and right ventricular work with a compensatory increase in stroke volume.

The mean VAS in Group 1 was 3.62 ± 0.39, in Group 2 was 2.48 ± 0.34. There was no statistically significant difference in the mean VAS scores in the four groups at 0 hours. The mean VAS scores at 4, 8, 12, 24 and 36 hours post-fentanyl infusion along with on demand rescue analgesia were least in Group 4 followed by Group 3, 2 and 1. This shows the analgesic efficacy of 40 μg/hr fentanyl infusion dose in Group 4. Thus, in terms of analgesic efficacy, 40 μg/hr epidural fentanyl dose is the 'optimal dose' along with 'on demand' 20 μg bolus dose of fentanyl. The analgesic efficacy of fentanyl can be attributed to supraspinal and spinal mechanisms.

The results support a segmental spinal effect of epidural fentanyl bolus administration and a nonsegmental dual spinal and supraspinal effect of epidural fentanyl infusion. They also provide evidence of clinical benefits from its predominant spinal action, notably improved analgesia, with a reduction in central side effects. The study thus provides support for a spinal mechanism of action of bolus administration of epidural fentanyl.

CONCLUSION

We thus conclude that epidural fentanyl dose of 40 μg/hr (Group 4) as "background infusion" is the most efficacious dose in terms of pain relief (analgesic efficacy) followed by 30 μg/hr (Group 3) and 20 μg/hr (Group 2), respectively along with patient's "on demand" rescue analgesia bolus dose of 20 μg in patients undergoing unilateral total knee replacement. Epidural fentanyl dose of 40 μg/hr is the "optimal dose" of background infusion along with patient control analgesia in terms of maximum analgesic efficacy, maximum hemodynamic stability and minimum side effects, in patients undergoing unilateral total knee replacement.

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