

Retrospective Analysis of Single-Dose Extended-Release Epidural Morphine Usage

Alparslan Turan^{1*}, Sheryar Sarwar¹, Stephen Sandwell², Kenneth Homolya³, Raghavendra Govinda³, Kimberly Williams RN⁴ and Laura Clark³

¹Department of Outcomes Research, The Cleveland Clinic, Cleveland, Ohio, USA

²University of Louisville, Cleveland, Ohio, USA

³Department of Anesthesiology, University of Louisville, Cleveland, Ohio, USA

⁴Acute Pain Service, Department of Anesthesiology, University of Louisville, Cleveland, Ohio, USA

Abstract

Objective: Moderate to severe postoperative pain is commonly experienced by surgical patients. A new advance in epidural anesthesia permits use of a 48 hour, extended release formulation of morphine (DepoDur™). This retrospective study examines efficacy and side effects of this drug used in two different doses.

Methods: 90 surgical patients were given Epidural analgesia, of which 31 and 59 patients were given single doses of 10 mg or 15 mg extended release formulations of morphine respectively. Following IRB approval, retrospective chart review focusing on supplemental pain medication needs of patients up to the first 48 hours after surgery was carried out. Pain medication doses were converted to morphine equianalgesic values using established equivalence formulas. Verbal analog pain scale records from postoperative recovery units were reviewed; side effects of patients were noted.

Results: During the first 48 hours after surgery, patients given 10 mg dosage of DepoDur™ required 27.3 ± 32.8 mg while those given 15 mg of DepoDur™ required 19.6 ± 18.2 mg of morphine ($P = 0.23$). Pain levels reported on a 0-10 scale at discharge after surgery were 1.6 ± 2.6 and 0.9 ± 1.5 for the 10 mg and 15 mg groups respectively ($P = 0.52$). Postoperative side effects were experienced in 77% and 68% of patients receiving a 10 mg and 15 mg dose of DepoDur™ respectively ($P = 0.46$). Postoperative nausea was reported with greater frequency at 65% and 46% in both 10 mg and 15 mg groups respectively ($P = 0.12$).

Conclusion: Comparing usage of 10 mg and 15 mg doses of DepoDur™ for extended release epidural analgesia, no significant difference was found in pain control, total pain medicine consumption during the first 48 hours after surgery and or incidence of any side effect.

Introduction

Despite ongoing efforts to curb postoperative pain, moderate to severe pain is experienced by as many as 88% of surgical patients within the first 24 hours after surgery of which 41% describe their pain as unbearable. 81% of postoperative patients in general report moderate to severe pain, with 29% of these patients also describing their pain as unbearable [1]. Uncontrolled pain adversely affects patient health causing delay in hospital recovery and ambulation [2], increased chronic pain development [3] and postoperative complications [4].

Commonly, postoperative pain may be treated using regional anesthesia, such as epidural and intravenous (IV) opiate administration [5]. Advantages of epidural anesthesia are early ambulation and related decrease in pulmonary complications [6,7], nausea and sedation compared to systemic opiate pain control [8-10]. Pain control is often better achieved using epidural anesthesia than with IV narcotics [12-15]. Patients show less of a stress response determined by lower circulating levels of epinephrine, norepinephrine, cortisol and serum glucose [11]. The drug of choice using epidural analgesia is local anesthetics but in the interest of improving efficacy of pain control, opioids are usually added. However epidural opioids may cause pruritis and urinary retention [10,12,14] and the risks associated with placing epidural catheters are low but may include epidural hematomas, infections and catheter migration into the thecal sac area [12].

Recent advances in epidural anesthesia allow use of a 48-hour extended release form of morphine, brand named DepoDur™ [16-18]. DepoDur™ uses DepoFoam™ technology delivering morphine as part of a multi-vesicular liposomal structure resembling foam [19]. As the

structure is broken down, embedded morphine is released providing longer periods of analgesia compared to regular epidural morphine dosages which provide 8 hours of pain relief [19,20]. Using extended release morphine, the need for supplemental opiates is decreased [21]. Similar to regular epidural morphine, pain control is better achieved than that with IV opiates although causing side effects such as nausea, pruritis, and hypotension [18,22]. However one study comparing 10 mg DepoDur™ doses to regular epidural morphine showed no significant difference in incidence of side effects [21]. Currently there are two available preparations of DepoDur™, 10 mg and 15 mg, and there is no clear consensus on which dose should be preferred. Furthermore, there is no study available comparing the two doses, not only for pain but also for side effects.

This retrospective study sets out to evaluate the effectiveness and side effects of two doses of epidural DepoDur™ assessing and comparing pain medicine consumption.

***Corresponding author:** Alparslan Turan, MD, Department of Outcomes Research, The Cleveland Clinic, 9500 Euclid Avenue, P-77, Cleveland, Ohio, USA, Tel: (216)-445-9857; Fax: (216) 444-6135; E-mail: alparslanturan@yahoo.com

Received May 16, 2012; Accepted June 30, 2012; Published July 05, 2012

Citation: Turan A, Sarwar S, Sandwell S, Homolya K, Govinda R, et al. (2012) Retrospective Analysis of Single-Dose Extended-Release Epidural Morphine Usage. J Anesth Clin Res 3:221. doi:10.4172/2155-6148.1000221

Copyright: © 2012 Turan A, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Methods

Following IRB approval and partial waiver from the IRB and Hospital Ethics Committee, charts from patients having received epidural DepoDur™ prior to operative procedures were retrospectively reviewed. The selected charts extended from December of 2006 through December of 2008.

Information obtained from the charts includes patient age, procedure, DepoDur™ dose, intra and postoperative analgesics, and postoperative verbal analog pain scores (VAPS). Adverse effects were also sought in chart review including incidence of respiratory depression, oxygen desaturation, nausea, vomiting, pruritis, urinary retention, constipation, pyrexia, and sensory or motor disturbances.

Standard protocol in our institution for patients receiving DepoDur™ included administration of 10 mg each of Montelukast and Loratadine prior to the procedure or day of surgery, and 10 mg of Loratadine on the day after the procedure. Intra-operative anti-emetics were recorded from the intra-operative anesthesia charts. Morphine and equivalent narcotic medicine usage was compared among DepoDur™ dosage groups as mean values \pm standard deviation (SD).

The student's t-test and the Pearson Chi-square test were used comparing continuous outcome (i.e., pain medicine consumption) and binary outcome (i.e., PCA usage and adverse side effects) amongst DepoDur™ dosage groups, respectively. Adverse effects were presented as a percentage of incidences and demographic data was presented as mean \pm SD.

Results

The average age of patients considered was 48 ± 11 years with greater majority of patients having under gone a gynaecological procedure, as shown in Table 1.

Table 2 compares both groups of patients, one receiving a 10 mg dose of epidural DepoDur™ (n=31) and the other 15 mg (n=59). Pain medication needs for both groups of patients were compared during three time periods; the intra-operative time period, the first two hours following surgery and lastly upto and including the first 48 post operative hours as shown in Table 2. A significantly higher average of morphine equivalent medication was given to the 15 mg group of patients during surgery ($P = 0.02$); although the group receiving 10 mg of DepoDur™ consistently required descriptively more pain medication during the first 48 hours post surgical period. The total 48 hour postoperative pain medication requirements were not different between the 10 and 15 mg groups (27.3 ± 32.8 and 19.6 ± 18.2 mg, respectively; $P = 0.23$) (Figure 1).

Further comparisons were made using data from patients with history of prior opiate use (n=10) vs. patients who were opioid naive (n=80) (Table 3). Patients with history of prior opiate use received

Variable	Summary statistics
Age (yrs)	48 ± 11
Female / Male (No.)	80 / 10
Body mass index (kg/m ²)	33 ± 16
Type of surgery (No.)	
Gynecologic	71
General	12
Genitourinary	5
Orthopedic	2

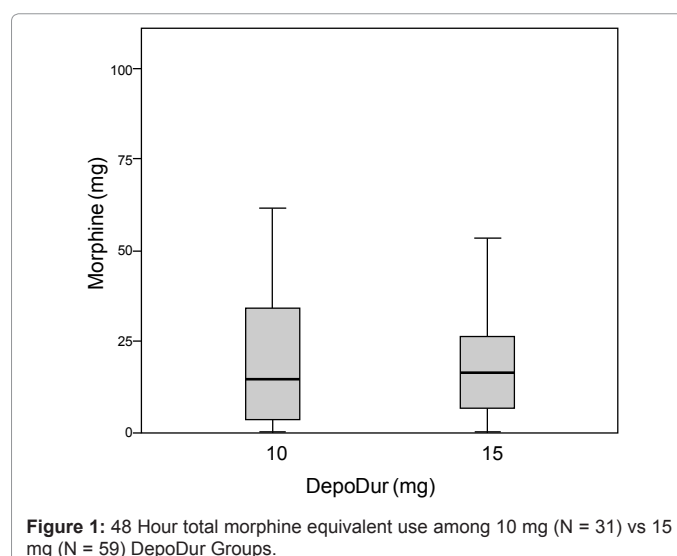
Table 1: Demographics and type of surgery (N = 90).

Time	DepoDur Dose (mg)	Opioid consumption † (mg; excluding DepoDur)	P	PCA Use (%)	P
Intra Operative	10	32.5 ± 13.5	0.02	N/A	N/A
	15	40.2 ± 17.2		N/A	
PACU (0-2 hrs)	10	12.3 ± 14.8	0.61	29	0.17
	15	10.8 ± 11.6		15	
Hospital Floor (2-48 hrs)	10	15.0 ± 26.0	0.22	39	0.08
	15	8.8 ± 12.4		20	
Post Operative (total 48 hrs)	10	27.3 ± 32.8	0.23	39	0.15
	15	19.6 ± 18.2		24	

† Morphine Equivalent

PACU = Post-anesthesia care unit, PCA = Patient controlled anesthesia

Table 2: Postoperative (morphine equivalent) (N = 31 and 59 for the 10 and 15 mg groups respectively).



lower dosages of epidural DepoDur™ ($P = 0.01$) and a lower amount of intra-operative pain medicine ($P < 0.001$) on average when compared to the opiate naive group, 11.5 ± 2.4 and 25.5 ± 7.1 vs. 13.5 ± 2.3 and 39.1 ± 16.6 mg, respectively. However, no difference in the amounts of morphine required during the postoperative period between patients with prior opiate use and opioid naive patients, 28.9 ± 29.8 vs. 21.4 ± 23.7 mg respectively ($P = 0.47$).

Patient controlled anesthesia (PCA) devices were required significantly more ($P = 0.03$) for patients with prior opioid use (60%) than for opioid naive patients (25%) respectively. The observed frequencies of PCA usage were also doubled in the 10 mg dose group as compared to the 15 mg dose group; however the differences were not statistically significant (Table 2). During the PACU recovery period, pain scores were descriptively lower among the 15 mg dose group at all time periods compared to the 10 mg dose group, but the differences were not statistically significant (Table 4). Side effects occurred in both 10 mg and 15 mg dose groups with 77% and 68% of patients experiencing one or more side effects respectively ($P = 0.46$, Table 5).

Discussion

This retrospective study sets out to evaluate the effectiveness and side effects of epidural DepoDur™, assessing and comparing pain medicine consumption amongst patients receiving the very same, using both 10 mg and 15 mg dosages. Although not statistically significant, this study does descriptively demonstrate greater efficacy with use of 15

Outcome	Opioid User (N = 10)	Opioid Naïve (N = 80)	P
DepoDur Dose (mg)	11.5 ± 2.4	13.5 ± 2.3	0.01
IntraOp pain medicine (mg) †	25.5 ± 7.1	39.1 ± 16.6	<0.001
Postop pain medicine (mg) †	28.9 ± 29.8	21.4 ± 23.7	0.47
PCA Usage	60%	25%	0.03
Side Effects	80%	70%	0.72

† Morphine Equivalent

Table 3: Compare patients with history of prior opiate use (n=10) and patients who were opioid naïve (n=80).

PACU Pain Scores	DepoDur Dose 10 (mg)	DepoDur Dose 15 (mg)	P
1 hour	3.8 ± 2.9	2.6 ± 3.1	0.14
2 hours	2.7 ± 2.4	2.2 ± 2.6	0.54
Discharge	1.6 ± 2.6	0.9 ± 1.5	0.52

Table 4: Pain score during PACU stay (N = 31 and 59 for the 10 and 15 mg groups respectively).

Side effect (%)	DepoDur Dose 10 (mg)	DepoDur Dose 15 (mg)	P
Respiratory Depression	10	5	0.41
Oxygen Desaturation	3	5	>0.99
Nausea	65	46	0.12
Pruritus	26	41	0.17
Other	3	3	>0.99
One or More	77	68	0.46

Table 5: Side effects occurred in both 10mg (N = 31) and 15 mg (N = 59) dose groups.

mg preparations compared to 10 mg preparations of DepoDur™. These findings are descriptively supported in the results which show lower consumption of opiate medications (Morphine Equivalent mg), lower usage of PCA and lower relevant Pain Scores at 1 and 2 hour intervals and discharge.

During the 48 hours following surgery, our results showed that no difference in supplemental pain medicine between patients randomized and receiving 10 and 15 mg dose of epidural extended release morphine, DepoDur™. At two separate time intervals, PACU (0-2 hrs) and Post-Operatively (total 48 hrs), patients receiving 10 mg of DepoDur™ required descriptively greater supplemental pain medication versus those patients receiving 15 mg DepoDur™; 12.3 ± 14.8 vs. 10.8 ± 11.6 (p = 0.61) morphine equivalent dosage for the initial PACU (0-2 hrs) period for 10 mg and 15 mg groups respectively, and 27.3 ± 32.8 vs. 19.6 ± 18.2 (p = 0.23) morphine equivalent dosage for the Post-Operative (total 48 hrs) period for both 10 and 15 mg groups respectively. The larger dose of epidural morphine was expected to provide better pain control and as anticipated this trend continued for the full 48 hours for which the product is reported to last. This finding may be partly attributed to the larger epidural dose and also because patients in the 15 mg group received a greater amount of systemic pain medication during the Intra-Operative period as opposed to patients in the 10 mg group, 40.2 ± 17.2 vs. 32.5 ± 13.5 (p = 0.02) respectively. The greater use of Intra-Operative systemic narcotics may have had a continued analgesic effect and extended into the PACU period thus contributing to reduced systemic pain medication requirements seen in the 15 mg dose group. In light of the aforementioned, several studies have also previously shown a reduction in the consumption of supplemental analgesics with the use of extended release formulations of morphine, DepoDur™, such as that seen in post-caesarean deliveries or after total hip/knee arthroplasties and lower abdominal surgeries [17,18,21,23].

Furthermore a second comparison, established between patients with previous history of opiate use prior to surgery (n=10) and those who were opiate naïve (n=80), showed the former group received a smaller dose of epidural DepoDur™ initially and also a lower amount of Intra-Operative pain medication compared to the opiate naïve group. Interestingly enough greater amounts of supplemental pain medication was however required in the 48 hour Post-Operative time period for patients with history of prior opiate use versus the opiate naïve patient population, 28.9 ± 29.8 vs. 21.4 ± 23.7 mg respectively (p = 0.47). With the standard deviation being large this was not unfortunately statistically significant. The sample size of the patient group presenting with histories of prior opiate use was only 10 and thus further study would be deemed necessary to establish a greater definitive observation. Side effect occurrence was also not different among these groups, 80% among those with a history of prior opiate use and 70% among the opiate naïve group (P = 0.72).

Patient controlled anesthesia (PCA) devices were required for patients with prior opioid use at double the frequency of opioid naïve patients, 60% (6/10) and 25% (20/80) respectively. They were also required more in the 10 mg dose group at also double the frequency (Table 2).

Results from the study also revealed usage of PCA was required in obtaining adequate pain control descriptively less frequently among the 15 mg dose group, 29% vs. 15% during the PACU (0-2hrs) period for both 10 mg and 15 mg groups respectively, and 39% vs. 24% during the Post-Operative (total 48 hrs) period also for both 10 mg and 15 mg groups respectively. These findings, as before, may also be attributed to the initially larger dose of DepoDur™ administered during the Intra-Operative time period and also a greater amount of supplemental morphine equivalent (mg) medication being given to the 15 mg dose group leading us to believe its lasting effects may have led patients to be less dependent on PCA. Interestingly, the larger dose was tolerated without a significant increase in side effects. In fact, overall incidence of one or more side effects was 77% and 68% amongst the 10 mg and 15 mg groups respectively. The most frequent side effect was nausea. Occurring with greater frequency in the 10 mg dose group when compared to the 15 mg group, 65% vs. 46% respectively, nausea may have been caused as a result of the systemic supplemental pain medications rather than the actual extended release epidural morphine. It is possible that because the 10 mg group required more supplemental systemic opioid medication, they may have experienced more nausea which is why we believe the 10 mg dose group also suffered greater respiratory depression, 10%, when compared to the 15 mg dose group, 5% (not significant P = 0.41).

Therefore we may conclude using a 15 mg dose of extended release epidural morphine might provide superior pain relief with less need for supplemental pain medicine during the 48 hour postoperative period when compared with a 10 mg dose group. Descriptively it is suggested those patients receiving 15 mg DepoDur™ experienced fewer side effects, however these findings are suggestive considering our small sample size. In lieu of these findings, it is our suggestion that further study is required before the findings can be deemed clinically significant. Seeing this is a retrospective study we have already included all the available data from all patients. An important limitation of this study is the small sample size. This retrospective study was limited by the sample size and further review of a greater number of patient outcomes would help better determine the efficacy and side effect profiles of epidural DepoDur™ at both 10 mg and 15 mg dosages.

References

1. Svensson I, Sjöström B, Haljamae H (2000) Assessment of pain experiences after elective surgery. *J Pain Symptom Manage* 20: 193-201.
2. Pavlin DJ, Chen C, Penaloza DA, Polissar NL, Buckley FP (2002) Pain as a factor complicating recovery and discharge after ambulatory surgery. *Anesth Analg* 95: 627-634.
3. Perkins FM, Kehlet H (2000) Chronic pain as an outcome of surgery, A review of predictive factors. *Anesthesiology* 93: 1123-1133.
4. Shea RA, Brooks JA, Dayhoff NE, Keck J (2002) Pain intensity and postoperative pulmonary complications among the elderly after abdominal surgery. *Heart Lung* 31: 440-449.
5. Rawal N, Sjöstrand U, Dahlström B (1981) Postoperative pain relief by epidural morphine. *Anesth Analg* 60: 726-731.
6. Rigg JR, Jamrozik K, Myles PS, Silbert BS, Peyton PJ, et al. (2002) Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. *Lancet* 359: 1276-1282.
7. Wijesundera DN, Beattie WS, Austin PC, Hux JE, Laupacis A (2008) Epidural anaesthesia and survival after intermediate-to-high risk non-cardiac surgery: a population-based cohort study. *Lancet* 372: 562-569.
8. Peyton PJ, Myles PS, Silbert BS, Rigg JA, Jamrozik K, et al. (2003) Perioperative epidural analgesia and outcome after major abdominal surgery in high-risk patients. *Anesth Analg* 96: 548-554.
9. Liu SS, Wu CL (2007) effect of postoperative analgesia on major postoperative complications: a systematic update of the evidence. *Anesth Analg* 104: 689-702.
10. Liu SS, Wu CL (2007) The Effect of Analgesic Technique on Postoperative Patient-Reported Outcomes Including Analgesia: A Systematic Review. *Anesth Analg* 105: 789-808.
11. Guay J (2006) The benefits of adding epidural analgesia to general anesthesia: a metaanalysis. *J Anesth* 20: 335-340.
12. Richman JM, Wu CL (2005) Epidural analgesia for postoperative pain. *Anesthesiol Clin North America* 23: 125-140.
13. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA, et al. (2003) Efficacy of postoperative epidural analgesia: a meta-analysis. *JAMA* 290: 2455-2463.
14. Flisberg P, Rudin A, Linner R, Lundberg CJ (2003) Pain relief and safety after major surgery. A prospective study of epidural and intravenous analgesia in 2696 patients. *Acta Anaesthesiol Scand* 47: 457-465.
15. Tsui SL, Law S, Fok M, Lo JR, Ho E, et al. (1997) Postoperative analgesia reduces mortality and morbidity after esophagectomy. *Am J Surg* 173: 472-478.
16. Angst MS, Drover DR (2006) Pharmacology of drugs formulated with depofom: a sustained release drug delivery system for parenteral administration using multivesicular liposome technology. *Clin Pharmacokinet* 45: 1153-1176.
17. Gambling D, Hughes T, Martin G, Horton W, Manvelian G (2005) A Comparison of depodur, a novel, single-dose extended-release epidural morphine, with standard epidural morphine for pain relief after lower abdominal surgery. *Anesth Analg* 100: 1065-1074.
18. Hartrick CT, Martin G, Kantor G, Koncelik J, Manvelian G (2006) Evaluation of a single-dose, extended-release epidural morphine formulation for pain after knee arthroplasty. *J Bone Joint Surg Am* 88: 273-281.
19. Viscusi ER, Martin G, Hartrick CT, Singla N, Manvelian G (2005) Forty-eight hours of postoperative pain relief after total hip arthroplasty with a novel, extended-release epidural morphine formulation. *Anesthesiology* 102: 1014-1022.
20. Alam M, Hartrick CT (2005) Extended-release epidural morphine (depodur): an old drug with a new profile. *Pain Pract* 5: 349-353.
21. Carvalho B, Roland LM, Chu LF, Campitelli VA, Riley ET (2007) Single-dose, extended-release epidural morphine (depodur) compared to conventional epidural morphine for post-cesarean pain. *Anesth Analg* 105:176-183.
22. Viscusi ER (2005) Emerging techniques in the management of acute pain: epidural analgesia. *Anesth Analg* 101: S23-S29.
23. Carvalho B, Riley E, Cohen SE, Gambling D, Palmer C, et al. (2005) Single-dose, sustained-release epidural morphine in the management of postoperative pain after elective cesarean delivery: results of a multicenter randomized controlled study. *Anesth Analg* 100: 1150-1158.