

Prospective randomized controlled study to compare the postoperative analgesic efficacy of intravenous dexmedetomidine and pethidine on patients undergoing lumbosacral spine surgeries

S Sindhuja

Assistant Professor, Dept. of Anaesthesia, KMCT Medical College, Kerala, India

*Corresponding Author: S Sindhuja

Email: sindhuja.ani@gmail.com

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Abstract

Introduction: Spine surgeries, especially spine fusion surgeries cause severe postoperative pain, hampering convalescence. This is a randomized double blind controlled study comparing the analgesic efficacy of postoperative intravenous pethidine and dexmedetomidine in patients undergoing lumbosacral spine surgeries.

Materials and Methods: After connecting patients to vital parameters monitor, patients were given general anaesthesia, induced with fentanyl 2mcg/kg, propofol 2mg/kg in graded doses and rocuronium 0.6mg/kg to facilitate tracheal intubation. All patients received 1 gram paracetamol iv slow infusion intraoperatively. After one and a half hours of surgery, injection fentanyl 1mcg/kg was repeated. After extubation and shifting the patients to PACU, patients were randomly allotted either group P/pethidine group or group D/dexmedetomidine group by computerised randomization. Group P patients received injection pethidine 0.5mg/kg loading dose diluted in 5 ml of distilled water slow iv, followed by 0.15mg/kg/hr infusion for 24hrs. Group D patients received injection dexmedetomidine 1mcg/kg bolus over 15 minutes followed by infusion of 0.5mcg/kg/min. Pulse rate, blood pressure, oxygen saturation, respiratory rate, VAS score and sedation score were monitored every 5 minutes for first 15 minutes, every 15 minutes for 1 hour, every hour till 6th hour, then 12th hour, and 24th hour.

Results: Dexmedetomidine has a faster on set of analgesic effect (10 minutes) compared to pethidine (30 minutes), provides better analgesia and manageable hemodynamics but, causes more sedation with an average sedation score of 2.83 compared to pethidine.

Conclusion: Dexmedetomidine is a better analgesic in the postoperative period compared to pethidine.

Keywords: Dexmedetomidine, Lumbosacral spine surgeries, Pethidine.

Introduction

Pain and suffering are an integral part of life. Now pain is recognised as the fifth vital sign. The Taxonomy Committee of International Association for the study of pain defines pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage".¹ Studies show that more than half of patients feel that postoperative pain is their primary concern.² The aims of postoperative pain relief include minimising pain, facilitating recovery, and preventing complications.³ Spine surgeries, especially spine fusion surgeries cause severe postoperative pain, hampering convalescence.⁴ Postoperative pain by itself is a risk factor for development of chronic pain syndromes.^{5,6} We anaesthesiologists have accepted the challenging task of providing pain relief.

Pethidine or meperidine is a synthetic opioid, which acts as an agonist at mu and kappa receptors. It is chosen for our study as part of my institutional practice and also because it produces effective analgesia, equipotent to morphine. It is also advantageous in suppressing postoperative shivering and producing less marked urinary retention and constipation.⁷

Dexmedetomidine, an imidazole compound, is the pharmacologically active dextroisomer of medetomidine that displays specific and selective α_2 adrenoceptor agonism. It is chosen for our study because of its several beneficial effects such as excellent analgesia, with lack

of respiratory depression and arousable sedation effect that helps in neurological assessment of the patient. It allows psychomotor function to be preserved while letting the patient to rest comfortably. The mechanism of action is unique and differs from clonidine. Post synaptic activation in central nervous system inhibits sympathetic tone and thus decreases blood pressure and heart rate.⁸⁻¹²

So in order to find a better post-operative analgesic, we in our study have compared the efficacy of pethidine and dexmedetomidine as post-operative analgesia in patients undergoing lumbosacral spine surgeries between May 2013 and April 2014.

Waleed M et al¹⁵ conducted a prospective randomized, double-blinded, controlled study, in which 39 patients with obstructive sleep apnea syndrome undergoing uvulopalatopharyngoplasty were assigned to dexmedetomidine group or Placebo group for postoperative analgesia. Onodera Y et al¹⁶ compared the methods used to achieve postoperative analgesia after abdominal aortic surgery with 15 patients each in fentanyl and dexmedetomidine group. Shahbaz R. Arain et al¹⁷ conducted a randomized study on 34 patients to check efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery, with 17 in each group. Hence, all the above references are similar to my study, so sample size of 40 each in both groups was taken to remove the bias due to inadequate sample size.

Materials and Methods

After obtaining clearance from the Institutional Ethical Committee, 80 patients, both male and female, in the age group of 18 to 70 years, belonging to American Society of Anaesthesiologists (ASA) classes 1 & 2, undergoing elective lumbosacral spine surgeries at Ganga medical centre, Coimbatore were enrolled in randomized double blind controlled trial. Patients with allergy to the drug being used, ASA 3 patients, ischaemic heart disease, elevated renal parameters and patients who had previously undergone spine surgery were excluded. The study was carried out from May 2013-April 2014. The statistical tests applied were mean, standard deviation and repeated ANOVA Test.

Standard preanesthetic evaluation was performed and informed consent was taken. All the patients were connected to the multiparameter monitors, that measured pulse rate, noninvasive blood pressure, electrocardiography, oxygen saturation and end tidal carbon dioxide. Patients were given general anaesthesia, induced with fentanyl 2mcg/kg, propofol 2mg/kg in graded doses, and rocuronium 0.6mg/kg to facilitate tracheal intubation. Injection ramosetron 0.3mg was also given. After intubation, air entry was checked if it was bilaterally equal, the cuff inflated and tube secured. Air entry rechecked after positioning. Intraoperatively pulse rate, blood pressure, oxygen saturation, respiratory rate and end tidal carbon dioxide were monitored every 5 minutes. The lungs were ventilated to obtain normocapnia that is ETCO₂ between 30 to 35mm Hg. Maintenance of anaesthesia was with sevoflurane or isoflurane along with nitrous oxide and oxygen. Titrated doses of rocuronium were given to maintain adequate muscle relaxation. All patients received 1 gram iv paracetamol intraoperatively. After one and a half hours of surgery, injection fentanyl 1mcg/kg was repeated. All the patients were reversed with injection glycopyrolate 0.01mg/kg and neostigmine 0.05mg/kg and extubated when fully awake, with sustained eye opening, obeying commands and regularly breathing with normal tidal volume.

All patients were transferred to post anaesthesia care unit and the baseline pulse rate, blood pressure, SpO₂, respiratory rate, visual analogue score for pain and sedation score were noted. All received oxygen 4 L/minute via face mask for 24 hrs. After confirming that

the baseline sedation score was less than 3, the patients were randomly allotted either group P/pethidine group or group D/dexmedetomidine group by computerised randomization. Group P patients received injection pethidine 0.5mg/kg loading dose diluted in 5 ml of distilled water slow iv, followed by 0.15mg/kg/hr infusion for 24hrs. This dose was chosen because Samina et al¹³ had given pethidine at the same dose for post operative analgesia in patients undergoing caesarean section. Also, in the study done by K. L. Austin et al,¹⁴ dose of pethidine was 25mg/hour. Even at this dose no significant toxic effects of norpethidine were observed and hence there is no risk of norpethidine toxicity in our study. Group D patients received intravenous dexmedetomidine 1 microgram/kg loading dose diluted in 20 ml given over 15 minutes via infusion pump followed by 0.5micrograms/kg/hr maintenance. The dose of dexmedetomidine was chosen according to studies done by Shahbaz R. Arain et al¹⁷ and Dholakia et al.²²

Both the patient and the anaesthesiologist in PACU recording the patient data were blinded from the drugs used for pain relief. Pulse rate, blood pressure, oxygen saturation, respiratory rate, VAS score and sedation score were monitored every 5 minutes for first 15 minutes, every 15 minutes for 1 hour, every hour till 6th hour, then 12th hour, and 24th hour. All patients received tablet Pantoprazole 40mg once daily. Patients who developed hypotension (systolic BP < 90 or mean arterial pressure < 60mmHg) were treated with fluids and vasopressors (ephedrine 6mg boluses), severe bradycardia (HR < 45) with injection atropine 0.6mg iv and vomiting with injection ondansetron 4mg. If patient became drowsy (sedation score > 3), infusion dose was reduced by 0.01mg/kg/hr for pethidine and by 0.1mcg/kg/hr for dexmedetomidine every 15 minutes till sedation score became < or = 3. When VAS was more than or equal to 5, rescue analgesic of Pethidine IV 10mg every 10 min was given in both groups until VAS becomes less than 5. All adverse effects were documented and treated.

Results

The two groups of patients were similar with respect to age, sex, weight & ASA status.

Table 1: Comparison of pulse rate (General linear model of repeated ANOVA)

Pulse Rate	Group(N=40 each)	Mean	Standard Deviation	F value	p Value
0 min	Pethidine	83.23	14.658		
	Dexmedetomidine	84.47	15.207		
5 min	Pethidine	80.82	14.479		
	Dexmedetomidine	74.10	14.311		
10 min	Pethidine	80.85	14.651		
	Dexmedetomidine	75.02	13.968		
15min	Pethidine	79.57	15.821		
	Dexmedetomidine	71.95	12.866		

30 min	Pethidine	77.80	14.941	2836.9	0.000
	Dexmedetomidine	69.55	12.504		
45min	Pethidine	76.40	14.221		
	Dexmedetomidine	67.93	12.303		
60 min	Pethidine	77.43	13.521		
	Dexmedetomidine	67.40	12.176		
2 hour	Pethidine	76.45	14.313		
	Dexmedetomidine	67.53	11.135		
3 hour	Pethidine	77.10	14.415		
	Dexmedetomidine	67.68	11.999		
4 hour	Pethidine	77.70	14.421		
	Dexmedetomidine	66.52	10.860		
5 hour	Pethidine	78.35	15.486		
	Dexmedetomidine	66.13	11.078		
6 hour	Pethidine	78.70	14.964		
	Dexmedetomidine	67.12	10.692		
12 hour	Pethidine	78.13	15.049		
	Dexmedetomidine	67.78	11.049		
24 hour	Pethidine	76.43	14.333		
	Dexmedetomidine	66.80	10.254		

Table 1 shows that the decrease in pulse rate among the dexmedetomidine group is significant as compared to pethidine group.

Table 2: Comparison of mean noninvasive blood pressure (General Linear model of Repeated ANOVA)

Mean Arterial Pressure	Group(N=40 each)	Mean	Standard Deviation	F value	p Value
0 min	Pethidine	95.5	14.9	6311.1	0.000
	Dexmedetomidine	95	11.0		
5 min	Pethidine	95.0	13.8		
	Dexmedetomidine	89.8	11.9		
10 min	Pethidine	95.0	14.2		
	Dexmedetomidine	86.1	10.3		
15min	Pethidine	110.8	15		
	Dexmedetomidine	97.2	12		
30 min	Pethidine	91.8	14.1		
	Dexmedetomidine	82.1	11.5		
45min	Pethidine	93.1	13.6		
	Dexmedetomidine	80.9	11.8		
60 min	Pethidine	92.6	11.8		
	Dexmedetomidine	81.1	9.5		
2 hour	Pethidine	90.2	12.4		
	Dexmedetomidine	80.3	9.7		
3 hour	Pethidine	89.7	11.0		
	Dexmedetomidine	78.5	9		
4 hour	Pethidine	86.4	9.4		
	Dexmedetomidine	83.3	12.4		
5 hour	Pethidine	87.5	9.4		
	Dexmedetomidine	82	13.1		
6 hour	Pethidine	86.9	9.2		
	Dexmedetomidine	80.6	12.3		
12 hour	Pethidine	88.4	10.1		
	Dexmedetomidine	80.5	12		
24 hour	Pethidine	89.5	11.2		
	Dexmedetomidine	80.7	12.0		

Table 2 shows that there was significant decrease in mean arterial pressure in dexmedetomidine group compared to pethidine group.

Table 3: Comparison of respiratory rate (General Linear model of Repeated ANOVA)

Respiratory rate	Group(N=40 each)	Mean	Standard Deviation	F value	p Value
0 min	Pethidine	14.87	1.842	10357.8	0.000
	Dexmedetomidine	15.45	1.947		
5 min	Pethidine	15.03	2.069		
	Dexmedetomidine	15.38	1.944		
10 min	Pethidine	15.27	1.921		
	Dexmedetomidine	15.50	1.695		
15min	Pethidine	15.33	1.900		
	Dexmedetomidine	15.13	2.015		
30 min	Pethidine	15.13	1.911		
	Dexmedetomidine	14.80	2.090		
45min	Pethidine	15.37	1.444		
	Dexmedetomidine	14.87	1.742		
60 min	Pethidine	15.15	1.442		
	Dexmedetomidine	14.75	1.794		
2 hour	Pethidine	15.23	1.405		
	Dexmedetomidine	14.73	1.894		
3 hour	Pethidine	15.23	1.368		
	Dexmedetomidine	14.95	2.264		
4 hour	Pethidine	15.25	1.565		
	Dexmedetomidine	14.63	2.047		
5 hour	Pethidine	15.25	1.613		
	Dexmedetomidine	14.90	1.985		
6 hour	Pethidine	14.75	1.498		
	Dexmedetomidine	14.60	1.795		
12 hour	Pethidine	14.93	1.366		
	Dexmedetomidine	14.82	1.583		
24 hour	Pethidine	14.72	1.240		
	Dexmedetomidine	14.60	1.499		

In Table 3 shows that though there was a mild decrease in respiratory rate in both the groups, the rate remained within normal range of 12 to 16/min.

Table 4: Comparison of VAS (General Linear model of Repeated ANOVA)

VAS score	Group(N=40 each)	Mean	Standard Deviation	F value	p Value
0 min	Pethidine	7.25	1.032	1575.6	0.000
	Dexmedetomidine	7.00	.934		
5 min	Pethidine	7.15	.834		
	Dexmedetomidine	5.27	.933		
10 min	Pethidine	6.05	1.377		
	Dexmedetomidine	4.23	1.271		
15min	Pethidine	5.55	1.339		
	Dexmedetomidine	2.97	1.387		
30 min	Pethidine	4.85	1.145		
	Dexmedetomidine	2.10	1.128		
45min	Pethidine	4.28	.960		
	Dexmedetomidine	1.70	.966		
60 min	Pethidine	3.43	1.083		
	Dexmedetomidine	1.65	.975		
2 hour	Pethidine	2.90	1.172		
	Dexmedetomidine	1.62	1.005		
3 hour	Pethidine	2.85	1.312		

	Dexmedetomidine	1.65	1.027		
4 hour	Pethidine	2.55	1.131		
	Dexmedetomidine	1.50	1.062		
5 hour	Pethidine	2.48	.933		
	Dexmedetomidine	1.45	.932		
6 hour	Pethidine	2.50	1.155		
	Dexmedetomidine	1.60	.871		
12 hour	Pethidine	2.32	1.047		
	Dexmedetomidine	1.58	.931		
24 hour	Pethidine	2.25	.870		
	Dexmedetomidine	1.78	1.000		

Table 4 shows that dexmedetomidine achieved a lower Visual analogue score compared to pethidine and at a faster rate.

Table 5: Comparison of sedation score (General Linear model of Repeated ANOVA)

Sedation score	Group(N=40 each)	Mean	Standard Deviation	F value	p Value
0 min	Pethidine	1.60	.496	5893.2	0.000
	Dexmedetomidine	1.68	.474		
5 min	Pethidine	1.62	.490		
	Dexmedetomidine	1.90	.304		
10 min	Pethidine	1.80	.405		
	Dexmedetomidine	2.03	.276		
15min	Pethidine	1.87	.335		
	Dexmedetomidine	2.48	.554		
30 min	Pethidine	1.93	.267		
	Dexmedetomidine	2.75	.707		
45min	Pethidine	2.03	.158		
	Dexmedetomidine	2.83	.636		
60 min	Pethidine	2.03	.158		
	Dexmedetomidine	2.70	.516		
2 hour	Pethidine	2.03	.158		
	Dexmedetomidine	2.65	.533		
3 hour	Pethidine	2.03	.158		
	Dexmedetomidine	2.65	.533		
4 hour	Pethidine	2.03	.158		
	Dexmedetomidine	2.70	.608		
5 hour	Pethidine	2.05	.221		
	Dexmedetomidine	2.65	.533		
6 hour	Pethidine	2.07	.267		
	Dexmedetomidine	2.65	.483		
12 hour	Pethidine	2.05	.221		
	Dexmedetomidine	2.55	.504		
24 hour	Pethidine	2.08	.267		
	Dexmedetomidine	2.37	.490		

Table 5 show that the sedation score goes on progressively increasing in the dexmedetomidine group rapidly as compared to the pethidine group.

Table 6: Comparison of requirement of rescue analgesia (by Pearson chi square test)

Group	No Rescue Analgesia required	Rescue Analgesia required	Total	χ^2 Value	p Value
Pethidine (N=40)	25(62.5)	15(37.5)	40(100)	18.462	0.000
Dexmedetomidine (N=40)	40(100)	0(0)	40(100)		
Total	65(81.25)	15(18.75)	80(100)		

Table 6 shows that 37.5% of the pethidine group patients required rescue analgesia while none required rescue analgesia in dexmedetomidine group.

Discussion

By analysis of variance we found that there was a significant difference in decrease in heart rate and mean arterial pressure in dexmedetomidine group compared to pethidine group. It is interesting to note that even in pethidine group 7 out of 40 (17.5%) patients had MAP > 110 mmHg, which can be attributed to no other reason but inadequate pain relief.

Regarding the effect of the drugs on visual analogue scale of patients, there was a 70% reduction in VAS in pethidine group and 80.8% in dexmedetomidine group which is statistically significant ($p < 0.001$). In addition, for the VAS to decrease to a value less than 5, on an average, it takes 30 minutes in pethidine group whereas, in dexmedetomidine group, it takes 10 minutes, which proves the faster onset of action of dexmedetomidine. Also 37.5% of the pethidine group required rescue analgesia while not single patient required rescue analgesia in Dexmedetomidine group.

Also, there was a rapid increase in sedation score in the dexmedetomidine group as compared to the pethidine group i.e. at the end of 45 min the sedation score is 2.03 in pethidine group while it is 2.83 in dexmedetomidine group and 40% patients requiring a reduction in the infusion dose because of the higher degree of sedation.

There are various studies who have obtained the results similar to the current study. Altindis NT et al¹⁸ studied that the addition of dexmedetomidine to pethidine in a patient-controlled analgesia (PCA) device reduced postoperative pethidine consumption when compared to pethidine alone, in 40 patients. Pethidine consumption with PCA was recorded until 24 hours postoperatively. Here, there was a mild insignificant decrease in heart rate and mean arterial pressure. Verbal rating score of pain in the PACU was lower in group I (Dexmedetomidine and pethidine group) than group II (pethidine group) ($p < 0.05$). Meperidine consumption was lower in group I than group II during the PACU stay and until 24 hours postoperatively ($p < 0.01$). This is similar to the current study.

The properties of pethidine intravenous infusion in postoperative period was studied by Mitsuhata H et al¹⁹ in 2012 who conducted a randomized double-blind controlled study comparing 10 patients receiving continuous intravenous pethidine infusion with 10 patients receiving continuous epidural infusion for postoperative analgesia after upper abdominal surgery. IV Group ($n = 10$) received 100 mg.24 h⁻¹ of pethidine intravenously and saline epidurally, Epi Group ($n = 10$) received 100 mg.24 h⁻¹ of pethidine epidurally and saline intravenously. It was found that there were no significant changes in pulse rate, blood pressure, respiratory rate and sedation scales from the baseline in

both the groups. This is in accordance with the current study with respect to pethidine characteristics.

Waleed M et al¹⁵ studied analgesic properties of dexmedetomidine infusion after uvulopalatopharyngoplasty in patients with obstructive sleep apnea. The results of the study were: Compared with placebo group, patients in the dexmedetomidine group required 52.7% less PCA morphine during the first 24 hours postoperatively, with significantly better visual analogue scale scores, less incidence of respiratory obstruction (5 vs. 12 patients, respectively; $P = .037$) and longer time to first analgesic request (21 (11) vs. 9 (4) minutes; $P = .002$) and higher sedation scores and lesser nausea and vomiting (7 vs. 24 patients, respectively; $P < 0.05$).

Shahbaz R. Arain et al¹⁷ conducted a randomized study on 34 patients undergoing elective inpatient who received either dexmedetomidine (initial loading dose of 1 microgram/kg over 10 min followed by 0.4 microgram/kg(-1) h(-1) for 4 h) or morphine sulfate (0.08 mg/kg) 30 min before the end of surgery up to 24 h. They too found that there was a decrease in heart rate, mean arterial pressure in dexmedetomidine group as compared to morphine group and required less morphine (PACU dexmedetomidine group, 4.5 +/- 6.8 mg; morphine group, 9.2 +/- 5.2 mg). Gurbet et al²⁰ did a randomized 40 patients undergoing total abdominal hysterectomy to receive either dexmedetomidine i.e. study group -loading 1 µg/kg over 30 minutes followed by infusion at 0.5 µg/kg/h until the end of surgery (same dose as the current study) or 0.9% saline i.e. control group (with the same infusion protocol) prior to the induction of anaesthesia. Here too patients reported better analgesia and sedation in dexmedetomidine group.

Feld et al²¹ conducted a pilot study among morbidly obese patients undergoing open gastric bypass surgery on post-operative analgesia while morphine was given as rescue analgesia. One group patients received 0.5 mcg/kg fentanyl on induction followed by fentanyl infusion (0.5 mcg/kg/h) until the end of surgery; and the other received dexmedetomidine (loading dose of 0.5 mcg/kg over 10 minutes prior to induction, followed by infusion at 0.4 mcg/kg/h). Dholakia et al²² conducted a retrospective study of patients undergoing laparoscopic bariatric surgery that compared a dexmedetomidine group (loading dose of 1 mcg/kg over 10 minutes followed by infusion at 0.2-0.7 mcg/kg/h until the end of surgery) with control group. The results of both studies were similar to our study.

The sedative properties of dexmedetomidine without affecting respiration was studied and proven by Martin E et al²³ who did double-blind, randomized, placebo-controlled, multicenter trial evaluating Dexmedetomidine for the sedation of 401 post surgical patients in an ICU. Dexmedetomidine was shown to have no effect on the respiratory rate, oxygen desaturation, duration of weaning, or time to extubation.

All the above detailed study references, that is, Altindis NT et al,¹⁸ Ekemen et al, Mitsuhata H et al,¹⁹ Waleed M et al,²⁰ Shahbaz R. Arain et al,¹⁷ Gurbet et al,²⁰ Feld et al,²¹ Dholakia et al²² and Martin E et al²³ show that their results were in accordance with current study. The dexmedetomidine group produced a decrease in heart rate and mean arterial pressure without significant decrease in respiratory rate with better analgesic property and sedative action as compared pethidine.

Conclusion

Dexmedetomidine is a better analgesic in the postoperative period compared to pethidine with a faster onset of analgesic effect compared to pethidine. Dexmedetomidine is a potent, highly selective and specific α_2 -adrenoreceptor agonist that has good analgesic property with manageable hemodynamic alterations and more sedation.

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