

Evaluation of efficacy of sedative and analgesic effects of single IV dose of dexmedetomidine in post-operative patients

Manasa CR^{1*}, Padma L², Shivshankar³, Ranjani Ramanujam¹

¹ Post graduate, Department of Pharmacology, ² Professor and Head, Department of Pharmacology,

³ Professor, Department of Anaesthesia,

Dr.B.R.Ambedkar Medical College, Kadugondanahalli, Bangalore, India.

ABSTRACT

Background: In the post-operative period, it has always been an important consideration for clinicians, to keep the patient comfortable, calm and pain free. So there is a constant need for an ideal sedative for postoperative patients. Alpha 2 adrenoreceptor agonists such as dexmedetomidine could provide an answer to this problem because they have several relevant physiological properties like sedation, anxiolysis, analgesia and arousability. Hence, the current study was undertaken to evaluate the efficacy of dexmedetomidine in post-operative patients in order to avoid polypharmacy.

Materials and Methods: Thirty patients who were operated under general anesthesia electively were randomly selected. All patients received 1 µg/kg bodyweight of dexmedetomidine intravenously with normal saline making up to 10 ml over 20 minutes. If the verbal numerical scale (VNS) of pain was mild (i.e. 1 to 3) one hour after extubation. The patients were assessed for degree and duration of sedation, hemodynamic changes, episodes of side effects, requirement of analgesics at every 5 min for first 30 min, every 10 min for next 1hr, every 15 min for next 1 h, and every 30 min for next 1h, every 1 h for 3h and 6th hourly till 24h. The need for rescue analgesic was noted.

Results: The mean duration of sedation was 129.6 ± 41.02 min, degree of sedation was -1 at 30 min, duration of analgesia 241.5 min, and mean degree of analgesia was 0 at 30 min, mean degree of sedation was -1. Mean time of administration of rescue analgesia was 170 min. Mean heart rate was 67.8 ± 5.24/min and mean arterial pressure was 78.0 ± 8.97mm of Hg, mean respiratory rate was 15.8 ± 2.33 breaths/min, mean partial pressure of oxygen SpO₂ was 99.5 ± 0.56%. No patient had any episode of shivering, vomiting, hypotension and respiratory depression.

Conclusion: Single IV dose of dexmedetomidine could provide adequate sedative, analgesic and anxiolytic effects with no accompanying respiratory depression, thereby minimizing polypharmacy.

Key words: Dexmedetomidine, Diclofenac, Post-surgical patients, Rescue analgesics, Postoperative patients, RASS scale, VNS scale.

Citation: Manasa CR, Padma L, Shivshankar, Ramanujam R. Evaluation of efficacy of sedative and analgesic effects of single IV dose of dexmedetomidine in post-operative patients. Int J Pharmacol and Clin Sci 2013;2:75-81.

INTRODUCTION

Pain, one of the most common symptoms experienced by surgical patients, has historically been poorly evaluated and frequently undertreated. The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”.^[1]

Postoperative pain differs from other types of pain in that, it is usually transitory, with progressive improvement over a relative short time

Received : 09 - 06 - 2013

Revised : 23 - 09 - 2013

Accepted : 30 - 09 - 2013

* Correspondence : manu_cr2001@yahoo.com

Conflict of interest: Nil

Source of support : Nil

Copyright: © 2013 Journal. All rights reserved.

course. Typically, the affective component tends towards anxiety state, associated with diagnosis of the condition, and fear of delay in provision of analgesic therapy by attendants.^[2]

The aim of postoperative pain treatment is to provide subjective comfort in addition to inhibiting trauma-induced nociceptive impulses in order to blunt autonomic and somatic reflex responses to pain and subsequently to enhance restoration of function by allowing the patient to breathe, cough and move more easily. Pain control may have a further benefit of improving clinical outcome by reducing the incidence of postoperative complications such as myocardial infarction or ischemia, risk of tachycardia and dysrhythmia, impaired wound healing, risk of atelectasis, thromboembolic events, peripheral vasoconstriction and metabolic acidosis.^[2]

Multiple agents, with different routes of administration are available for effective management of acute pain. Analgesic agents include opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and local anaesthetics. Less traditional agents that may be used more frequently in the future include clonidine, dexmedetomidine, dextromethorphan, and gabapentin. Routes of administration include the oral, parenteral, epidural, and intrathecal routes.^[3]

Keeping the patient comfortable, calm and pain free during the postoperative period, has always been an important consideration for clinicians. The use of drugs like nitrous oxide, propofol, fentanyl and midazolam for sedation can cause hemodynamic changes, respiratory and cardiovascular depression. So there is a constant need for an ideal analgesic and sedative for postoperative patients. Alpha 2 adrenoceptor agonists such as dexmedetomidine could provide an answer to this problem because they have several relevant physiological properties like sedation, anxiolysis, analgesia and

arousability.^[4,5] In addition, it does not cause clinically relevant respiratory depression.^[6,7]

Because of these properties (sedation, lack of respiratory depression, and analgesia sparing), dexmedetomidine might prove useful in the postoperative period for patients having major surgical procedures that are associated with significant pain.

Hence, the aim of the current study was to explore the effects of dexmedetomidine in post-operative patients.

MATERIALS AND METHODS

Study design

It was a prospective open labeled study. This study was conducted between October 2010 to November 2012 with informed consent of the patient or patient's attender and was approved by institutional ethics committee of Dr.B.R.Ambedkar Medical College, Bangalore. 30 patients who were operated under general anaesthesia (GA) electively were randomly selected. One day prior to the study, patients were educated about the verbal numerical scale (VNS) and its use depending on the severity of pain.

After extubation, patients were connected to a cardiac monitor and basal recordings such as pain score using Verbal numerical scale (VNS)^[7], sedation score using Richmond agitation sedation scale (RASS)^[6] and hemodynamic changes like heart rate and blood pressure were noted. If pain score was mild according to VNS i.e.1-3, then patients were given dexmedetomidine 1 µg/kg in normal saline making up to 20ml over 15 min. Then the pain score, sedation score, heart rate, blood pressure, partial pressure of oxygen (SpO₂), respiratory rate were monitored for every 5 min for first 30 min, every 10 min for next 1hr, every 15 min for next 1 h, every 30 min for

next 1h, every 1 h for 3h and 6th hourly till 24h. The need or the time of administration of rescue analgesic diclofenac was noted in each patient.

Inclusion and exclusion criteria

After ethics committee clearance, a total of 30 patients aged between 18-65 y of either sex belonging to American society of Anaesthesiology (ASA) grade I & II post-operative patients done under general anaesthesia were included in the study. Patients on ventilator with cardiovascular, respiratory, hepatic, renal diseases, neurological diseases or with history of convulsions, psychiatric disease, hypotension and shock, or on antihypertensives, with ASA grade III & IV were excluded from the study.

Efficacy parameters

Primary efficacy endpoints include duration and degree of sedation, duration and degree of postoperative analgesia, hemodynamic monitoring and need for rescue analgesia.

Degree of sedation was assessed using RASS i.e., +4: combative, violent, danger to staff, +3: pulls or removes tube or catheter; aggressive, +2: frequent non purposeful movements, fights ventilator, +1: anxious, apprehensive, but not aggressive, 0: Alert and calm, -1: awakens to voice (eye opening or contact), -2: light sedation, briefly awakens to voice (eye opening), -3: moderate sedation, movement or eye opening, -4: deep sedation, no response to voice, but movement or eye opening to physical stimulation, -5: unarousable, no response to voice or physical stimulation. Degree of pain was assessed using VNS i.e. 1-3: mild pain, 4-6: moderate pain, 7-10: severe pain and to the worst imaginable pain.

Secondary efficacy end points include episodes of shivering, post-operative side effects such as hypotension (< 60 mm Hg), bradycardia (< 60 beats/min) and episodes of respiratory depression (< 10 breaths/min).

Statistical analysis:

A total of 40 patients were taken allowing 7% drop out rate to yield 90% power and study population were analysed. The protocol population excluded patients who were considered un-evaluable because of protocol violations. The data was tabulated and analysed using descriptive statistical tool. Mean, standard deviation was done by student 't' test. Complete analysis was carried out using SPSS package version 3.2.

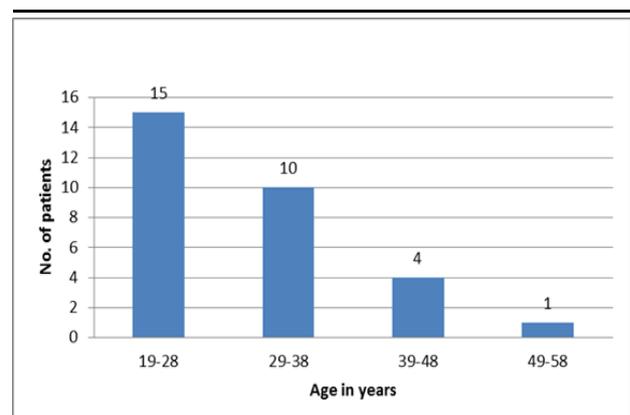
RESULTS

Fourty patients were assessed for eligibility, of whom 30 met the inclusion criteria. The baseline characteristics were similar in all the patients (Table 1) with common age group of 19-28 years (Fig. 1).

Table 1: Different types of surgical cases included in the study

Operations	No. of patients
Left mastoidectomy with tympanoplasty	7
Diagnostic laparoscopy	1
Laparoscopic cholecystectomy	1
Laparoscopic tubectomy	4
Laparoscopic appendectomy	2
Excision of the accessory breast tissue	5
Laparoscopic salphingo-oophorectomy	2
Septoplasty	2
Functional endoscopic sinus surgery	2
Second degree burns	3
Ear reconstruction	1

Figure 1: Age distribution of the study subjects



Mean duration of sedation was 129.6 ± 41.02 min, mean degree of sedation was -1, mean duration of analgesia was 139 min (Fig. 2), mean time for administration of rescue analgesics was 169 min (Fig. 3) i.e. the time by which all the patients took another analgesic after the initial analgesic effect waned off.

Figure 2: Mean duration of analgesic effect in minutes.

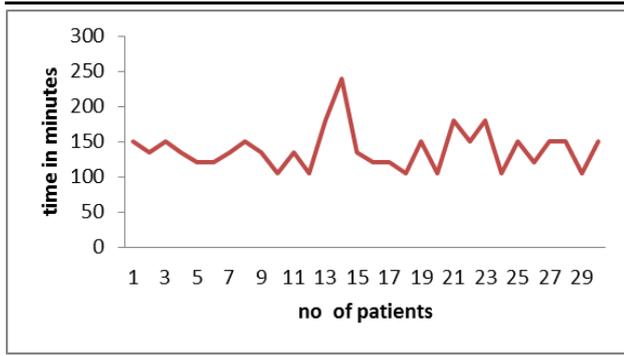
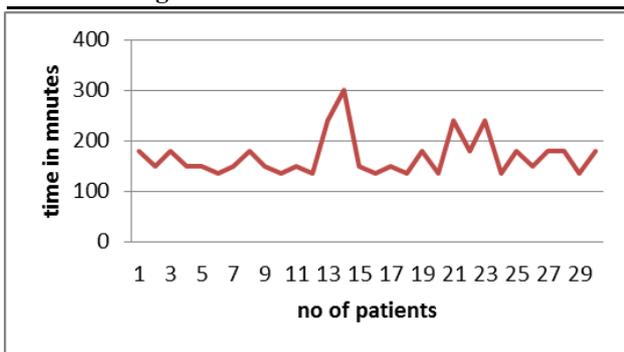


Figure 3: Mean time of administration of rescue analgesics.



Mean heart rate was 67.8 ± 5.24 beats/min, mean MAP was 78.0 ± 8.97 mm Hg, mean respiratory rate was 15.8 ± 2.33 breaths/min, mean SpO₂ is $99.5 \pm 0.56\%$. No patient had any incidence of shivering, hypotension and respiratory depression. Only one patient had an episode of bradycardia, which was 48 breaths/min and was treated with atropine 4mg IV stat.

DISCUSSION

This study was conducted to find the sedative and analgesic effects of dexmedetomidine in post-operative patients.

In the current study, the mean duration of sedation of dexmedetomidine was $129.6 \pm$

41.02 min. The elimination half-life is 2-3 h, with half-life ranging from 4 minutes after a 10 minute infusion to 250 minutes after an 8h infusion. In another study by Scheinn et al,^[8] post-operative patients sedated with dexmedetomidine display pharmacokinetics similar to that seen in volunteers.^[8] In the present study, mean degree of sedation was -1 which is different from the results of Aho et al^[9] and Venn et al.^[10]

In the present study, mean duration of analgesia was 139 min; mean time of administration of rescue analgesics was 169 min. The findings of the study by Cortinez et al^[11] comparing the analgesic effect of dexmedetomidine with remifentanyl were similar to that of our study. In a noxious heat versus pain intensity plot obtained in a group of volunteers, dexmedetomidine was less effective in reducing pain than remefentanyl. Also, the slope was different, suggesting different mechanism of action and an effect from sedation.

In our study, almost all patients required diclofenac as a rescue analgesic. But in a comparative trial done in post-operative patients after major isurgery showed that patients receiving dexmedetomidine required significantly less morphine to control postoperative pain ($p < 0.01$) than the morphine-treated group.^[12]

In the present study, mean heart rate was 67.8 ± 5.24 beats/min and mean MAP was 78.0 ± 8.97 mm of Hg. Ebert et al^[13] performed a study on volunteers using a target controlled infusion system to provide increasing concentration of dexmedetomidine (0.7 to 15 ng/ml). The lower two concentrations produced a decrease in MAP (13%) followed by progressive increase 12%) in MAP. Increasing concentrations of dexmedetomidine also produce decrease in heart rate (29%) and cardiac output (35%). Bloor et al^[14] showed that infusion of

dexmedetomidine in volunteers resulted in compensated reduction in systemic sympathetic tone without changes in the baroreceptor sensitivity. A biphasic hemodynamic response was observed with a bolus dose of dexmedetomidine in humans in the study conducted by Ebert et al,^[14] an acute I.V. injection of 2 mcg/kg of dexmedetomidine resulted in initial increase in blood pressure (22%) and decrease in heart rate (27%) from baseline after injection. The initial increase in blood pressure was probably due to vasoconstrictive effects of dexmedetomidine following stimulation of peripheral α_2 receptors. Heart rate returned to baseline by 15 minutes, and blood pressure gradually declined to approximately 15% below baseline by 1 h.^[15]

Mean respiratory rate was 15.8 ± 2.33 breaths/min and mean SpO₂ was $99.5 \pm 0.56\%$. Another study done by Ebert and colleagues, showing infusions of dexmedetomidine in concentrations of 15 ng/ml showed no change in arterial oxygenation or pH in spontaneously breathing volunteers. At highest concentrations, PaCO₂ increased by 20%. Respiratory rate increased with increasing concentration from 14 breaths/minute to 25 breaths/minute; when dexmedetomidine and propofol were titrated to equal sedative end points (BIS of 85), there was no change in the respiratory rate in both.^[13] In a study by Cortinez et al^[11] showing the comparative effects of ramifentanil and dexmedetomidine on respiratory parameters in normal volunteers, the hypercapnic ventilator response was unaffected even at doses that produced unresponsiveness to vigorous stimulation. PaCO₂ increased mildly with dexmedetomidine, but it reached a plateau after the first increment.

In the current study, patients were calm and comfortable throughout the study period. α_2 receptor - subtype C found mainly in central nervous system, is responsible for anxiolytic effect of dexmedetomidine.^[19] No patients had any episode of shivering, vomiting, hypoten-

sion and respiratory depression. Only one patient had an episode of bradycardia in dexmedetomidine group, which was 48 and was treated by giving atropine 0.6 mg IV.

A study conducted by Maxwell to investigate the respiratory effects of clonidine reported that there is lack of respiratory depression in patients with α_2 adrenoceptor agonists.^[20] In a study done by Shabaz R, Talke Chen and Talke Richardson et al^[12, 21] demonstrates that early postoperative HR was significantly slower in the dexmedetomidine treated patients due to decrease in the central sympathetic outflow, catecholamine release and also due to vagomimetic action. Also, there was a decrease in postoperative agitation and anxiety in all patients. An open-label, randomized study done by Maldonado J R^[17] et al clinical investigation suggests that postoperative sedation with dexmedetomidine was associated with significantly lower rates of postoperative delirium and lower care costs.

The main limitations of our study is the small sample size; a large sample size would give more reliable result. A comparison with a control would help in assessing anxiety appropriately.

A single IV dose of Dexmedetomidine provides adequate sedative, analgesic & anxiolytic effects with no accompanying respiratory depression, thereby minimizing polypharmacy. Since a single drug provides multiple properties, dexmedetomidine could be one of the better alternatives in the post-operative patients. Though analgesia is adequate, rescue analgesics may be required in patients who have diminished pain threshold, as it has a very short plasma half-life .

ACKNOWLEDGEMENT

we are grateful to Anesthesia department of Dr.B.R.Ambedkar Medical College, Bangalore and Themis Lab for their valuable help in conduction and sponsoring the study drug.

REFERENCES

1. Boyd D, Butler M, Carr D, Cohen M, Devor M, Dworkin R, et al. IASP Taxonomy. [Internet]. 1994 [cited 2013 Aug 18]. Available from: http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Definitions#Pain
2. Aitkenhead A, Smith G, Rowbotham D. Textbook of Anaesthesia. 3rd ed. US : Churchill Livingstone; 2006.p.435-44.
3. Miller RD, Eriksson LI, Fleisher L, Wiener-Kronish J, Young WL. Miller's anaesthesia-volume 2. 7th ed. US: Churchill Livingstone; 2009.p.2757-8.
4. Hall JE, Uhrich TD, Barney JA, Arian SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small dose dexmedetomidine infusions. *Anesth Analg* 2000;90:669-705.
5. Aho MS, Erkola OA, Scheinin H, Lehtinen AM, Kortilla KT. Effect of intravenously administered dexmedetomidine on pain after laparoscopic tubal ligation. *Anesth Anal* 1991;73:112-8.
6. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002;166:1338-44.
7. Bijur PE, Latimer CT, Gallagher EJ. Validation of a verbally administered numerical rating scale of acute pain for use in the emergency department. *Acad Emerg Med* 2003;10:390-2.
8. Scheinin H, Aantaa R, Anttila M, Hakola P, Helminen A, Karhuvaara S. Reversal of the sedative and sympatholytic effects of dexmedetomidine with a specific alpha₂-adrenoceptor antagonist Atipamezole: A Pharmacodynamic and kinetic study in healthy volunteers. *Anesthesiology* 1998;89:574-84.
9. Aho M, Erkola O, Kallio A, Scheinin H, Kortilla K. Comparison of dexmedetomidine and midazolam sedation and antagonism of dexmedetomidine with Atipamezole. *J Clin Anesth* 1993;5:194-203.
10. Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit. Patient and clinician perceptions. *Br J Anaesth* 2001;87:684-90.
11. Cortinez LI, Hsu YW, Sum-Ping ST, Young C, Keifer JC, Macleod D, et al. Dexmedetomidine pharmacodynamics: Part II: Crossover comparison of the analgesic effect of dexmedetomidine and remifentanyl in healthy volunteers. *Anesthesiology* 2004;101:1077-83.
12. Arain SR, Ruehlow RN, Uhrich TD, Ebert TJ. The Efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. *Anesth Analg* 2004;98:153-8.
13. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colincio MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology* 2000;93:382-94.
14. Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology* 1992;77:1134-42.
15. Talke P, Chen R, Thomas B, Aggarwall A, Gottlieb A, Thorborg P, et al. The hemodynamic and adrenergic effects of perioperative dexmedetomidine infusion after vascular surgery. *Anesth Analg* 2000;90:834-9.
16. Aho M, Lehtinen AM, Erkola O, Kallio A, Kortilla K. The effect of intravenously administered dexmedetomidine on perioperative hemodynamics and isoflurane requirements in patients undergoing abdominal hysterectomy. *Anesthesiology* 1991; 74:997-1002.
17. Maldonado JR, Wysong A, Vander-Starre PJ, Block T, Miller C, Reitz BA. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery; *Psychosomatics* 2009;50:206-17.
18. Marcou TA, Marque S, Mazoit JX, Benhamou D. The Median Effective Dose of Tramadol and Morphine for Postoperative Patients: A Study of Interactions. *Anesth Analg* 2005;100:469-74.

19. Hunter JC, Fontana DJ, Hedley LR, Jasper JR, Lewis R, Link RE, et al. Assessment of the role of alpha2-adrenoceptor subtypes in the antinociceptive, sedative and hypothermic action of dexmedetomidine in transgenic mice. *Br J Pharmacol* 1997;122:1339-44.
20. Venn RM, Hell J, Grounds RM. Respiratory effects of dexmedetomidine in surgical patients requiring intensive care: *Crit Care* 2000;4:302-8.
21. Talke P, Richardson CA, Scheinin M, Fisher DM. Postoperative pharmacokinetics and sympatholytic effects of dexmedetomidine. *Anesth Analg* 1997;85:1136-42.
