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Research Article

A randomized, open-labelled study of the sedative, analgesic and anxiolytic effect of dexmedetomidine and tramadol in postoperative patients

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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. This prospective, randomized trial was conducted to compare the safety and efficacy of dexmedetomidine and tramadol in the management of postoperative pain.
Methods: In the present study 60 patients operated under general anaesthesia with a pain score of 1-3 were randomly allocated into two groups to receive either dexmedetomidine (group D) or tramadol (group T). In both groups, pain score, sedation score, heart rate, blood pressure, SPO_2, 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 the next 1 h, every 1 h for 3 h and 6th hourly till 24 h. The need for rescue analgesic was also noted. The data were tabulated and analysed using descriptive statistical tool. Mean, standard deviation and comparison between the groups was done by student's 't' test. A p value less than 0.0001 was considered significant.
Results: Mean duration of sedation of dexmedetomidine was 129.6±41.02 and for tramadol was 117.3 ± 47.75 (p=0.14), mean degree of sedation in both group was -1, mean duration of analgesia 139 min in Group D and 280 min in Group T (p<0.0001), rescue analgesia was required at 169th min in Group D and 288th min in Group T (p<0.0001), mean heart rate in Group D was 67.8±5.24 and 69.4±4.79 (p=0.12), mean Mean Arterial Pressure (MAP) in Group D was 78.0±8.97 and in Group T was 89.2±10.63 (p<0.00001), mean respiratory rate in Group D was 15.8±2.33 and in Group T was 15.9±2.09 (p=0.41), mean SPO_2 in Group D was 99.5±0.56 and in Group T was 99.4±0.62 (p=0.14). There was no significant difference in degree and duration of sedation, duration of analgesia, vital parameters, and adverse effects in both groups but there was a statistical difference in the duration of analgesia and the need for rescue analgesia in Group D.
Conclusion: Though there is no statistical difference in both groups, dexmedetomidine significantly reduced anxiety, agitation and produced calmness in postoperative patients which was not seen with tramadol.

Key words: Dexmedetomidine, Tramadol, Postoperative patients, Rescue analgesics, RASS scale, VNS scale

INTRODUCTION

Pain is a multifaceted and very subjective experience.[1] 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."[2] It not only results in major distress to patients, but also adversely affects the endocrine and immune function, which can negatively affect wound healing and cardiopulmonary and thromboembolic diseases. Considering that postoperative pain is one of the most frequently reported postoperative symptoms, effective pain management can significantly affect the outcome of the surgery.[1] Postoperative pain differs from other types of pain in that, it is usually transitory, with progressive improvement over a relative short time 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.[3]

Preexisting pain, anxiety, age, and type of surgery are the four most significant predictive factors for the intensity of postoperative pain, and the type of surgery, age, and psychological distress are the three most important predictive factors for postoperative analgesic consumption. Additionally, the type of surgery is a strong

predictor for both postoperative pain and analgesic consumption.[1]

Although it is an acknowledged fact that postoperative pain is frequently encountered in clinical practice, inadequate management of pain is common and can be associated with many negative outcomes like deep vein thrombosis, pulmonary embolism, coronary ischemia, myocardial infarction, pneumonia, poor wound healing, insomnia, and demoralization.[4]

Therefore, effective management of postoperative pain is imperative, to improve the surgical outcomes and prevent postoperative complications. Additionally, this is required not only to provide subjective comfort but also to inhibit trauma-induced nociceptive impulses to enable blunting of autonomic and somatic reflex responses to pain and as a result, enhance restoration of function by allowing the patient to breathe, cough and move more easily.[5]

Multiple agents, with different routes of administration are available for effective management of acute pain. Analgesic agents include opioids, like tramadol and pentazocine, nonsteroidal anti-inflammatory drugs (NSAIDs) like ketorolac and diclofenac, 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.

Dexmedetomidine is a congener of clonidine and acts as a centrally acting α2 agonist. It is currently used often during the perioperative period because of its haemodynamic, sedative, anxiolytic, analgesic, neuroprotective and anaesthetic sparing effects. Additionally, it has the advantages of minimal respiratory depression with cardioprotection, neuroprotection and renoprotection.[6] It is 8 times more specific for α2 adrenoceptors than clonidine (ratios of α2:α1 activity, 1620:1 for dexmedetomidine, 220:1 for clonidine),[7] thus minimising the unwanted side effects because of α-1 receptors. Additionally, it is highly selective to α-2A receptors which mediate analgesia and sedation, making it especially useful in anaesthetic practice. Dexmedetomidine is useful in blunting haemodynamic responses in the perioperative period because of its central sympatholytic effect. However, this effect can cause bradycardia and hypotension as the major side effects.[6]

Tramadol is one of the most frequently used drugs in our hospital for postoperative analgesia. It is an atypical opioid with a dual mode of action involving weak agonistic action at peripheral and central μ-opioid receptors and nonopioid mechanism by modifying transmission of pain impulses at the spinal level because of inhibition of noradrenaline uptake and stimulation of serotonin release.[8,9] This drug provides safe analgesia during the postoperative period and is longer acting than diclofenac sodium, which is one of the most frequently used NSAID. Additionally, it does not cause respiratory depression unlike other opioids.[8]

Hence, we conducted this study to compare the efficacy and safety of dexmedetomidine with that of tramadol in post-operative patients.

METHODS

This is a prospective, randomized, open-labelled study. It was conducted for a period of one year between November 2011 and October 2012. Patients aged between 18-65 years of either sex belonging to American Society of Anesthesiologists (ASA) grade I and II post-operative patients operated 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, on antihypertensives with ASA grade III and IV were excluded from the study.

Preanaesthetic evaluation was done on the previous day and was educated regarding verbal numerical scale (VNS) to point out on the scale depending on the severity of pain. Patients were assigned to receive either dexmedetomidine (group D) or tramadol (group T), based on a computerized randomization chart.

After extubation, patients were connected to cardiac monitor and basal recordings such as pain score, sedation score and hemodynamic changes such as heart rate, blood pressure and respiratory rate and partial pressure of oxygen were noted. If pain score was mild (1-3), then group D was given dexmedetomidine 1 mcg/kg in normal saline making up to 20 ml intravenously (I.V.) over 15 min and group T was given tramadol 50 mg I.V. with normal saline making up to 20 ml over 15 min. Then, the pain score[10], sedation score, heart rate, blood pressure, SPO_2, respiratory rate were monitored every 5 min for the first 30 min, every 10 min for the next 1 h, every 15 mins for the next 1 hr, every 30 min for the next 1 hr, every 1 hr for the next 3 h and 6th hourly till 24 h. The need for rescue analgesic was noted in each group.

The primary endpoints were duration and degree of sedation, duration and degree of postoperative analgesia, hemodynamic monitoring and need for rescue analgesia. The secondary endpoints included incidence of shivering, episodes of post operative side effects such as hypotension (mean arterial non-invasive blood pressure [NIBP] fall <60 mmHg), bradycardia (<60 beats/min) and episodes of respiratory depression (<10 breaths/min).

The degree of sedation was assessed using RASS (Richmond agitation sedation scale, see table 1).[11]

Post-operative pain was assessed using the verbal numerical scale (VNS, see figure 1).[10] The patient was

asked to quantify their pain by using the VNS pain scores with 0 corresponding to no pain, 1-3 mild pain, 4-6 moderate pain, 7-10 severe pain and 10 to the worst imaginable pain. In our study, 0=0, 1-3=1, 4-6=2, 7-10=3.

The study was approved by the hospital ethical committee and written informed consent was obtained from all the patients.

A total of 70 patients were taken allowing 7% drop out rate to yield 90% power. Two study populations were analyzed. The per protocol population excluded patients who were considered un-evaluable because of protocol violations. The data were tabulated and analysed using descriptive statistical tool. Mean, standard deviation and comparison between the groups was done by student's 't' test. A p value less than 0.0001 was considered significant. Complete analysis was carried out using SPSS package version 3.2.

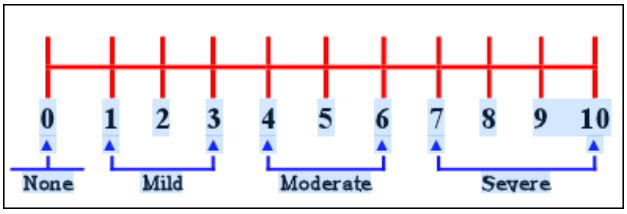

Figure 1: Verbal numerical scale to assess degree of pain.

RESULTS

Seventy patients were assessed for eligibility, of whom 60 met the inclusion criteria and were randomised equally to group D or group T (n=30 in each of the groups; see figure 2).

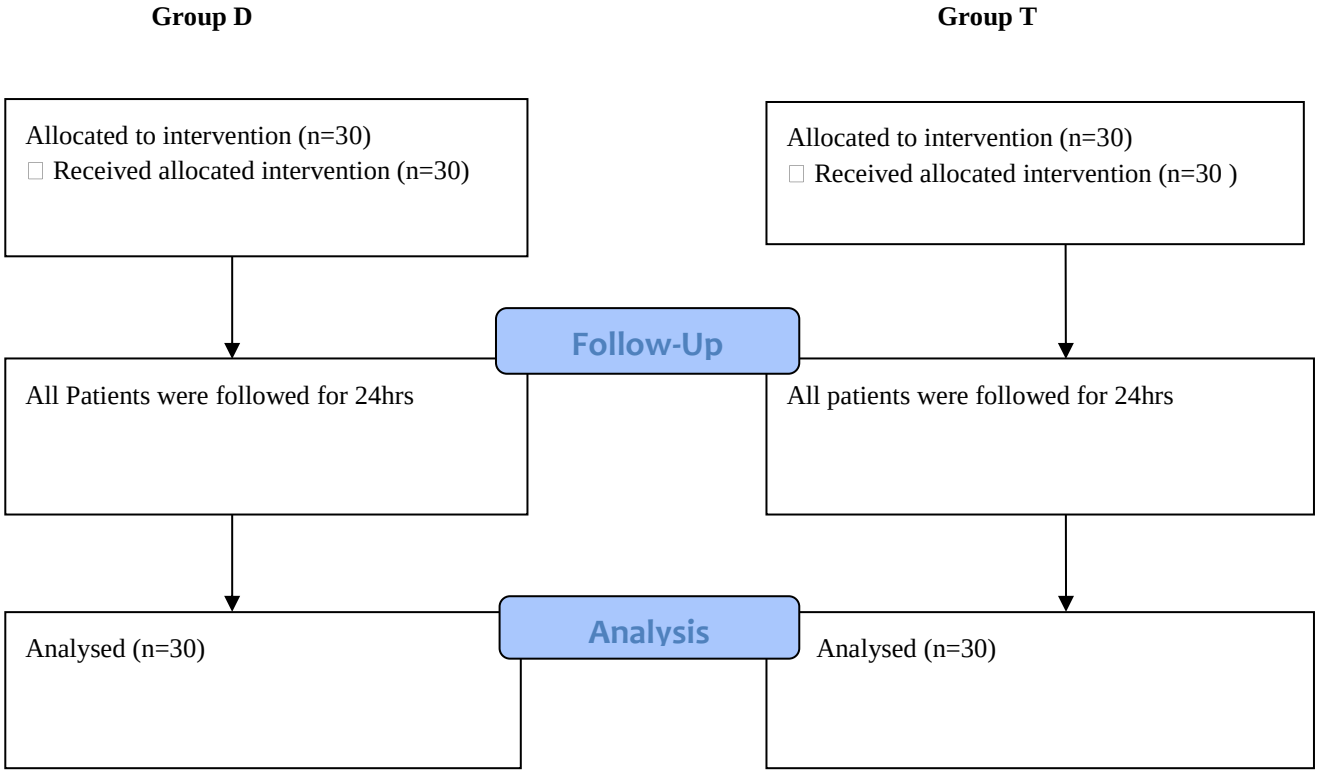

Figure 2: Study design.

There was no significant difference in the patients' characteristics in both the groups (see Table 1).

Mean duration of sedation of dexmedetomidine was 129.6±41.02 min and for tramadol 117.3±47.75 min (p=0.14), mean degree of sedation in both groups -1, mean duration of analgesia 139 min in Group D and 280 min in Group T (p<0.0001; see figure 3), mean time for administration of rescue analgesics is 169 min in Group D and 288 min in Group T (p<0.0001; Figure 4), mean heart rate in Group D was 67.8±5.24 beats/min and in Group T 69.4±4.79 beats/min (p=0.12), mean MAP in Group D 78.0±8.97 mmHg and in Group T was 89.2±10.63 mmHg (p<0.00001), mean respiratory rate in Group D is 15.8±2.33 breaths/min and in Group T is 15.9±2.09 breaths/min (p=0.41), mean SpO2 in Group D is 99.5±0.56% and in Group T is 99.4±0.62% (p=0.14).

Both treatment regimens were well-tolerated during the study. No patients had any incidence of shivering, hypotension and respiratory depression in both groups. Only one patient had incidence of bradycardia in dexmedetomidine group, which was 48 beats/min and was treated by giving atropine.

Table 1: Baseline characteristics.

Parameters	Group D	Group T
Age	19-55	20-58
Sex	M-17 F-13	M-18 F-12
Types of operation		
Left mastoidectomy with tympanoplasty	7	6
Diagnostic laparoscopy	1	2
Laparoscopic cholecystectomy	1	1
Laparoscopic tubectomy	4	3
Laparoscopic appendicectomy	2	3
Excision of the accessory breast tissue	5	4
Laparoscopic salphingo-oophorectomy	2	3
Septoplasty	2	2
Functional endoscopic sinus surgery (FESS)	2	2
Second degree burns	3	2
Ear reconstruction	1	2

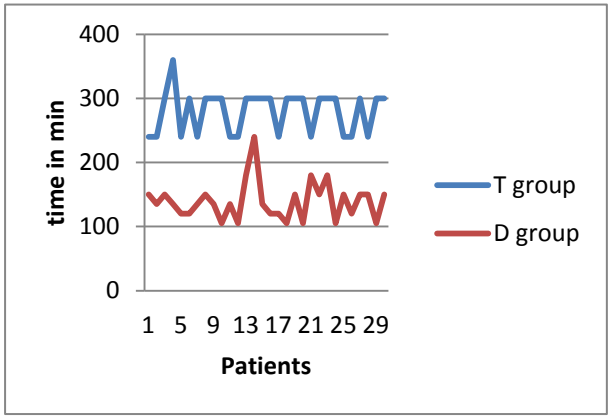

Figure 3: Mean duration of analgesia.

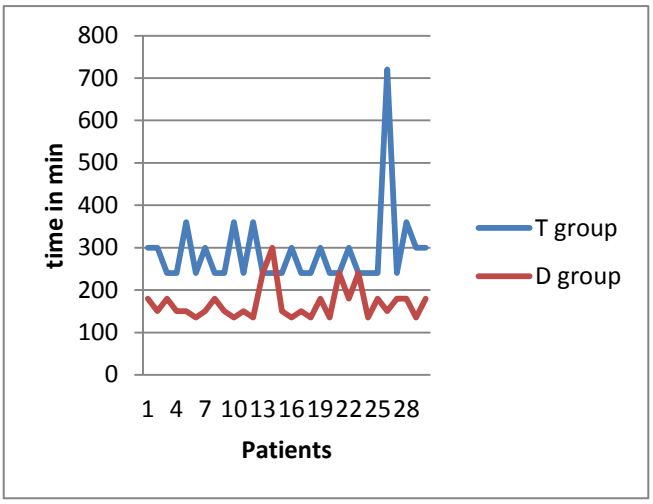

Figure 4: Time of administration of rescue analgesics.

DISCUSSION

The current study was conducted to compare the sedative and analgesic effects of dexmedetomidine with that of tramadol in postoperative patients.

In the current study, the mean duration of sedation of dexmedetomidine was 129.6±41.02 min and for tramadol 117.3±47.75mins (p=0.14), and the mean degree of sedation in both groups was -1. Two phase 3, European, multicenter, randomized, double-blind studies comparing dexmedetomidine with midazolam (MIDEX trial) and with propofol (PRODEX trial) also showed similar findings with a RASS score of -1 and -0.9 respectively.[12] Although the difference in the degree of sedation between both groups was not statistically significant, the duration of sedation was longer in group D, compared to group T although not statistically significant (p=0.14).

In the present study mean duration of analgesia was 139 min in Group D and 280 min in Group T (p <0.0001) and mean time of administration of rescue analgesics was 169th min in Group D and 288th min in Group T (p <0.0001). The duration of analgesia was found to be significantly more in Group T than Group D and the time of administration of rescue analgesia was significantly earlier in Group D compared to Group T. The findings of the study by Cortinez et al[13] comparing the analgesic effect of dexmedetomidine with remifentanil 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 remefentanil. Also, the slope was different, suggesting a different mechanism of action and an effect from sedation. Venn et al.[14] have shown that postoperative analgesic requirements were reduced by 50% in cardiac patients, and the need for rescue medication for sedation (midazolam) was diminished by 80%. According to another study by Arain et al,[15] patients were given either dexmedetomidine or tramadol after major in-patient surgery, and those who received dexmedetomidine

required significantly less morphine as rescue medication than the morphine-treated group (p<0.01).

In the present study, mean heart rate in Group D is 67.8±5.24 and 69.4±4.79 (p=0.12) and mean MAP in group D 78.0±8.97 and in group T is 89.2±10.63 (p<0.0001). There was no statistically significant difference in mean MAP and heart rate. Ebert et al[16] 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%). Increasing concentrations of dexmedetomidine also produced decreases in heart rate (29%) and cardiac output (35%). Infusion of dexmedetomidine in volunteers also has been shown to result in compensated reduction in systemic sympathetic tone without changes in the baroreceptor sensitivity.[17] A biphasic hemodynamic response was observed with a bolus dose of dexmedetomidine in humans in the study conducted by Ebert et al.[10]: 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 base line that occurred at every 5 minutes after injection. The initial increase in blood pressure was probably due to vasoconstrictive effects of dexmedetomidine when stimulating peripheral α2 receptors. Bloor et al.[17] showed that infusion of dexmedetomidine in volunteers resulted in compensated reduction in systemic sympathetic tone without changes in the baroreceptor sensitivity. In a study by Talke et al,[18] during emergence from anesthesia, heart rate was slower with dexmedetomidine (73±11 bpm) compared to the placebo group (83±20 bpm; p=0.006), and the percentage of time the heart rate was within the predetermined hemodynamic limits was higher in the dexmedetomidine group (p<0.05). Additionally, plasma norepinephrine levels increased only in the placebo group and were significantly lower for the dexmedetomidine group during the immediate postoperative period (p=0.0002). These postoperative changes in heart rate and blood pressure are important factors determining the outcome especially in high-risk patients like those who undergoing vascular surgery or coronary artery bypass graft surgery.[18]

Dexmedetomidine has minimal respiratory side effects.[7] Belleville et al.[19] demonstrated obstructive apnea episodes in patients receiving high doses of dexmedetomidine. This was seen more commonly with doses of 1 or 2 μg/kg given over 2 minutes, which were meant to produce rapid sedation. Probably the apnea and irregular breathing pattern was because of the deep sedation and anatomical features of the patients rather than because of the drug.[7] In our study, the mean respiratory rate was not significantly different in both groups (p=0.41). Ebert et al,[16] also showed that infusions of dexmedetomidine up to concentrations of 15 ng/mL in spontaneously breathing volunteers showed no change in arterial oxygenation or pH. At highest concentrations, PaCO2 increased by 20%. Respiratory rate increased with increasing concentration from 14 breaths/minute to 25 breaths/minute.[20] When dexmedetomidine and propofol were titrated to equal sedative end points, both resulted in no change in the respiratory rate.[21] In a study by Hsu et al.[22] showing the comparative effects of remifentanil 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 plateau after the first increment. Most sedative agents, especially opioids are associated with the danger of respiratory depression and often have to be discontinued during the extubation period, whereas a dexmedetomidine can be infused safely in the extubated, spontaneously breathing patient.[7]

In the current study, patients in dexmedetomidine group were calm and comfortable compared to patients in tramadol group. The α2 B subtype C receptor found mainly in central nervous system is responsible for anxiolytic effect.[23] We also found that both treatments were well-tolerated, with no patients having any incidence of shivering, vomiting, hypotension and respiratory depression in both groups. Only one patient had bradycardia in the dexmedetomidine group and was treated by giving atropine.

To conclude, according to our study, dexmedetomidine and tramadol are similar in terms of post-operative sedation and analgesia. However, the former has the added advantage of reducing anxiety, agitation and also producing a calming effect, making it a promising agent in this clinical setting. Although tramadol is used very commonly as a postoperative analgesic, there are no studies that we found comparing dexmedetomidine with tramadol. Because of the multiple effects produced by dexmedetomidine, it could be used as one of the better alternatives in the postoperative period with the additional advantage of reducing polypharmacy. However, the limitations of our study are that the sample size is small and also it was not a double-blinded trial. Therefore, a larger randomized, double-blind trial comparing the safety and efficacy of dexmedetomidine with tramadol is required.

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