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Original article:

A Randomised Comparative Study to Evaluate the Efficacy and Safety of Dexmedetomidine Infusion Versus Morphine Infusion for Sedation in Mechanically Ventilated Post-Operative Patients Admitted to The Intensive Care Unit

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Abstract:

Background: The ICU caters to a wide variety of critically ill patients afflicted with various medical illnesses, post-operative conditions, severe trauma, and poisonings etc. many of whom are on mechanical ventilation. Appropriate and adequate sedation decreases agitation, anxiety and the stress response and improves the tolerance for routine ICU procedures. Both excessive and inadequate sedation can increase morbidity and canhave adverse effect on length of ICU stay. A patient focused and protocol-based management is therefore important to manage sedation.

Materials & Methods: The study was a randomized comparative trial done on patients admitted post-operatively to the Intensive Care Unit of the Department of Anaesthesiology and Intensive Care, VMMC and Safdarjung Hospital, New Delhi, after due clearance from the Hospital Ethical Committee. 80 Post-operative patients of age 18 to 60 years of either sex and APACHE II Score of <25, admitted to the ICU requiring mechanical ventilation were selected for the study and randomly divided into two groups using computer generated random numbers table: Dexmedetomidine group (group D) and Morphine group (group M). Oversedation was defined as RASS <-3 and undersedation as >0. A RASS of 0 to -3 was considered as the target (appropriate) sedation. In both the groups, the study drugs were administered for 24 hours and after that patients were sedated as per the existing protocols of the ICU.

Results: Our study showed that demographic profile such as age, sex, body weight and APACHE II score was statistical non-significant. The incidences of over sedation as well as under sedation were observed more in group M with p=0.0341. Patients in group M were observed to have a significantly lower pain visual analogue score (VAS) between T4 to T16 (p<0.05).

Conclusion: Dexmedetomidine has significant analgesic action but is inferior to morphine in this respect. Adequate sedation and analgesia with either Dexmedetomidine or Morphine can help in preventing incidences of delirium in critically ill patients.

Keywords: ICU, Dexmedetomidine, Morphine, RASS, Mechanical Ventilation.

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INTRODUCTION

The ICU caters to a wide variety of critically ill patients afflicted with various medical illnesses, post-operative conditions, severe trauma, and poisonings etc. many of whom are on mechanical ventilation. These patients need special medical attention, intensive monitoring and management especially during the initial periods of admission.

The patients in ICU are exposed to a variety of stress like multiple tubings and monitors, invasive therapies and procedures like mechanical ventilation, endotracheal suctioning, catheterization, physiotherapy, bed making and wound dressing besides being bedridden for a considerable duration.[1] This often causes pain, anxiety and agitation ; resulting in increased stress, patient ventilator dyssynchrony, increase in oxygen demand and inadvertent removal of devices and catheters which can increase the morbidity, mortality and length of stay (LOS) in ICU.

Therefore, patients in the ICU usually require adequate sedation with analgesia as an essential aspect of the treatment. Appropriate and adequate sedation decreases agitation, anxiety and the stress response and improves the tolerance for routine ICU procedures. Appropriate sedation in patients on mechanical ventilation, allows manipulation of ventilator parameters and helps in synchronized breathing resulting in a better outcome and early extubation.[2]

Administration of sedatives while monitoring the effect with a valid scoring system is the chief modality of providing sedation. It also involves other approaches in combination including good communication, regular reassurance, environmental control and management of thirst, hunger and full bladder etc.[3]

An ideal sedative agent should have both sedative and analgesic effects, minimal adverse effects, rapid onset and offset, should not accumulate in renal or hepatic dysfunction, should not have active metabolites or interactions with other ICU drugs and should also be cheap.

Traditionally, a number of drugs have been used for sedation in the ICU e.g. Opioids (Morphine, Fentanyl), Benzodiazepines (Midazolam), Propofol etc.

Morphine is the most commonly used drug for sedation in the ICU in our institution. It is a time tested and effective drug which is cheap and easily available. The major adverse effects limiting its use are respiratory depression, gastrointestinal dysmotility and psychotic symptoms like hallucinations in some cases.[4]

A comparatively new drug being used now days for sedation in ICU is Dexmedetomidine, an alpha-2 adrenoceptor agonist like clonidine with eight times more affinity (primarily the α2A receptor). Dexmedetomidine has become popular sedative agent in ICU because of its ability to produce ‘cooperative sedation’ or ‘arousable sedation’. The patients remain awake, calm, are able to communicate their needs and natural sleep is maintained. Dexmedetomidine has both sedative and analgesic sparing effects, reduces delirium and agitation and causes minimal cardiorespiratory adverse effects, facilitating early weaning from ventilator.[5] Unlike Morphine and other conventional sedatives, Dexmedetomidine is claimed to be associated with fewer adverse effects on other systems. Due to these, Dexmedetomidine is has been recommended and increasingly being used worldwide as the sedative of choice for sedation in the ICU.[6] This study was assessed to the efficacy and safety of Dexmedetomidine for sedation in mechanically ventilated post-operative patients in the ICU compared to Morphine.

MATERIALS & METHODS

The study was a randomized comparative trial done on patients admitted post-operatively to the Intensive Care Unit of the Department of Anaesthesiology and Intensive Care, VMMC and Safdarjung Hospital, New Delhi, after due clearance from the Hospital Ethical Committee.

Patient Selection and Study Drugs Administration

After taking written informed consent from the accompanying attendants, 80 Post-operative patients of age 18 to 60 years of either sex and APACHE II Score of <25, admitted to the ICU requiring mechanical ventilation were selected for the study and randomly divided into two groups using computer generated random numbers table: Dexmedetomidine group (group D) and Morphine group (group M).

- **Group D:** received inj. Dexmedetomidine infusion. 200 µg of Dexmedetomidine was diluted in 0.9% Sodium Chloride and administered as loading intravenous infusion of 1µg/kg over 10-20 minutes, followed by a maintenance infusion of 0.2-0.7 µg/kg/hr using a controlled infusion device.
- **Group M**: received Morphine infusion. 30 mg ampoule of Morphine was diluted in 0.9% Sodium Chloride and given as loading intravenous infusion of 100µg/kg over 10-20 minutes, followed by maintenance infusion of 10–70 µg/kg/hr.

The rate of the maintenance infusion was adjusted to achieve the target sedation score (RASS) of 0 to -3.

Fentanyl bolus of 50 to 100µg intravenously was kept as rescue sedation for patients in either group not adequately sedated and Haloperidol, 0.03 to 0.15 mg/kg intravenously was kept as the rescue drug for agitation.

Oversedation was defined as RASS <-3 and undersedation as >0. A RASS of 0 to -3 was considered as the target (appropriate) sedation. Hypotension was defined as either systolic blood pressure <90 mmHg or mean blood pressure <60 mmHg and bradycardia was considered with heart rate <60 beats per minute.

In both the groups, the study drugs were administered for 24 hours and after that patients were sedated as per the existing protocols of the ICU.

Inclusion Criteria

1. Post-operative patients of either sex 18 to 65 years of age admitted to the ICU requiring mechanical ventilation for ≥ 24 hours.
2. APACHE II scores <25

Exclusion Criteria

1. Patients who were hemodynamically unstable with severe bradycardia (heart rate<50 bpm) or Hypotension (Mean arterial pressure <60 mm Hg) despite appropriate intravenous volume replacement and vasopressors.
2. Patients with neurological diseases, active seizures.
3. Patients with acute myocardial ischemia, second- or third-degree heart block etc.
4. Diabetic patients with uncontrolled blood sugar levels.
5. Morbidly obese patients.
6. Patients with hepatic dysfunction (Childs-Pugh classification B or C).
7. Patients with renal dysfunction (serum creatinine > 2mg/dl).

8. Known allergy to the study drugs.

Monitoring and Assessment

1. The primary efficacy outcome studied was proportion of time spent in the target sedation range (RASS score 0 to -3).

2. Pain assessed using the Visual Analogue Scale (VAS).

3. Heart rate, Blood pressure, Respiratory rate, ECG, Oxygen saturation, Temperature, Ventilator readings etc. were monitored before and during the administration of the drugs at 5min.,15 min.,30 min.,60 min. and then two hourly after the loading dose.

4. Occurrence of delirium as defined by the ICD 10 Classification of Mental and Behavioral Disorders: Diagnostic criteria for research, WHO, 1993.

5. Response to weaning from mechanical ventilation or extubation (if applicable).

6. Pathological investigations including hematological and liver and renal function tests, ABGs, and urine output were compared.

7. Any adverse drug reactions to the study drugs.

Statistical Analysis

The data collected was fed in computer and analyzed using Microsoft excel and SPSS statistical software version 21. The statistical significance between the two groups for quantitative variables was detected by unpaired t test or Non parametric Mann-Whitney test. For qualitative variables, Chi square or Fisher exact test were used. A p value ≤ 0.05 was considered statistically significant.

RESULTS

Our study showed that demographic profile such as age, sex, body weight and APACHE II score was statistical non-significant in table 1.

Patients in group M received loading dose of 100 µg/kg followed by mean dose ranging from 19.49 to 29.95 µg/kg/hr. In group D received a loading dose of 1µg/kg/hr followed by a mean dose of 0.24 to 0.32 µg/kg/hr (Figure 1).

The mean RASS score was statistically similar in both the groups across same points of time (Table 2). The patients in group D remained within target sedation levels (RASS 0 to -3) for longer duration as compared to group M but the difference was not statistically significant (table 3).

The incidences of over sedation as well as under sedation were observed more in group M with p=0.0341 (table 4).

The initial mean systolic, diastolic and mean Blood pressures (at T0) were similar in both groups (p = 0.067, 0.344, and 0.168 respectively) while significant differences were observed in the course of treatment with group D showing lower mean values between T2 to T24 (p value ranging from 0.02 to < 0.001) at different times (figure 2). Hypotension was seen more in patients in group D (45%) versus group M (17.5%) (p=0.015). Maximum patients developed hypotension around 6 hours after start of infusion in both the groups (figure 3). Also, Bradycardia (heart rate <60 beats per minute) was seen in more patients in group D: 9(22.5%) as compared to group M: 1 (2.5%) which was significant with a p value of 0.014 (fig 4).

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Patients in group M were observed to have a significantly lower pain visual analogue score (VAS) between T4 to T16 ($p<0.05$) (Figure 5).

Table 1: Comparison of Demographic parameters

	Group D (N=40)	Group M (N=40)	P-value
Age (yrs)			
Mean age	39.88 ± 13.96	37.63 ± 15.82	0.444
Sex			
Female	16(40.00%)	17(42.50%)	1.00
Male	24(60.00%)	47(58.75%)	
Body weight			
Mean	58 ± 6.46	57.35 ± 8.16	0.694
APACHE II score			
Mean	7.83 ± 3.65	8.93 ± 3.05	0.148

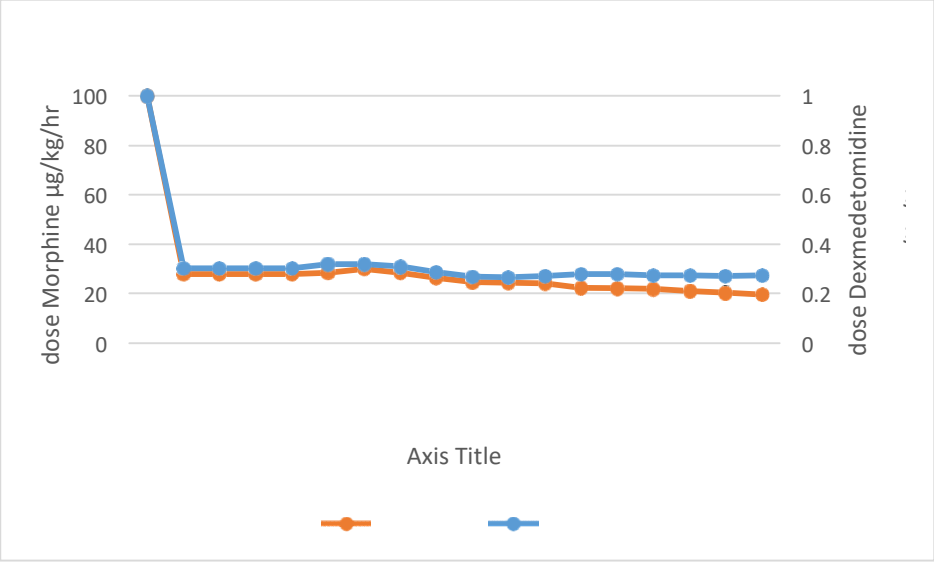

Figure 1: Mean dose

Table 2: RASS score (Mean± SD)

Time	Group D	Group M	P value
T0	-2.3 ± 0.97	-2.2 ± 1.04	0.658
T5min	-2.3 ± 0.97	-2.2 ± 1.04	0.658
T15 min	-2.3 ± 0.97	-2.15 ± 1.1	0.519
T30min	-2.13 ± 0.91	-1.83 ± 1.15	0.200
T1	-1.68 ± 0.83	-1.53 ± 1.15	0.506
T2	-1.25 ± 0.93	-1.15 ± 1.08	0.657
T4	-0.85 ± 0.92	-1.03 ± 1.25	0.478
T6	-0.85 ± 1.08	-0.85 ± 1.25	1.000
T8	-0.7 ± 0.94	-1.1 ± 1.19	0.100
T10	-0.55 ± 1.04	-1 ± 1.15	0.070
T12	-0.5 ± 0.82	-0.95 ± 0.85	0.018
T14	-0.63 ± 0.74	-0.88 ± 1.02	0.213
T16	-0.73 ± 0.64	-0.83 ± 0.81	0.543
T18	-0.83 ± 0.64	-0.8 ± 0.85	0.882
T20	-0.65 ± 0.7	-0.68 ± 0.76	0.879
T22	-0.6 ± 0.59	-0.53 ± 0.55	0.560
T24	-0.48 ± 0.68	-0.48 ± 0.55	1.000

Table 3: Average time spent in target sedation level in hours

	Mean ± SD	Median	Range	p value
Group D	22.65 ± 1.9	24.00	17 - 24	0.327
Group M	22.26 ± 1.6	22.00	18 – 24	

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Table 4: Incidences of Oversedation and Undersedation

	Group D	Group M	Total
Oversedation	5(12.50%)	13(32.50%)	18(22.50%)
Undersedation	15(37.50%)	18(45.00%)	33(41.25%)

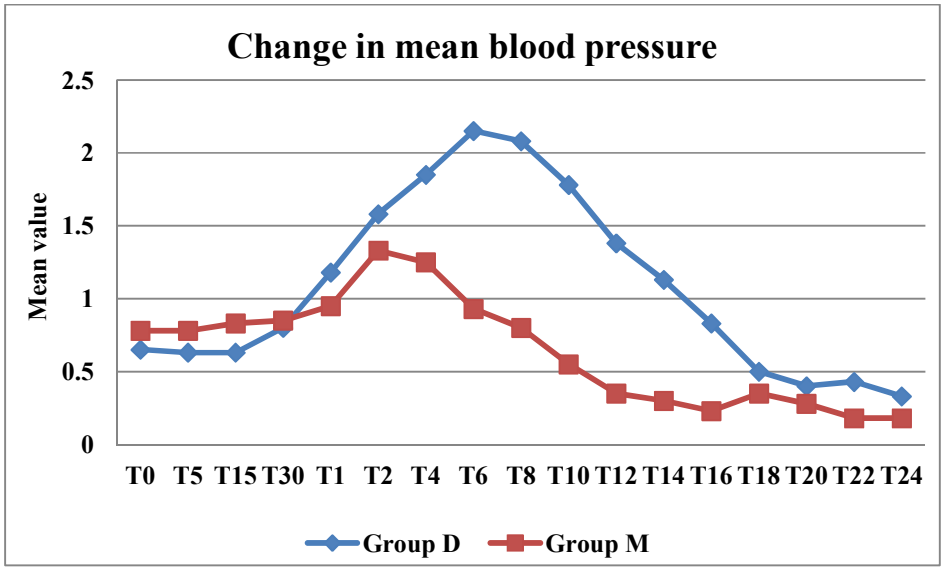

Figure 2: Change in mean blood pressure

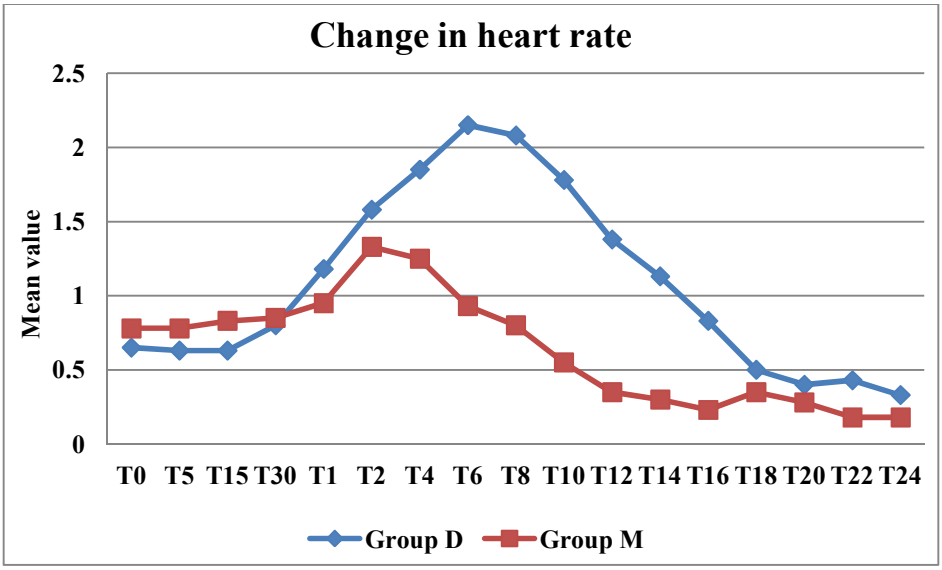

Figure 3: Changes in Heart Rate (beats/min)

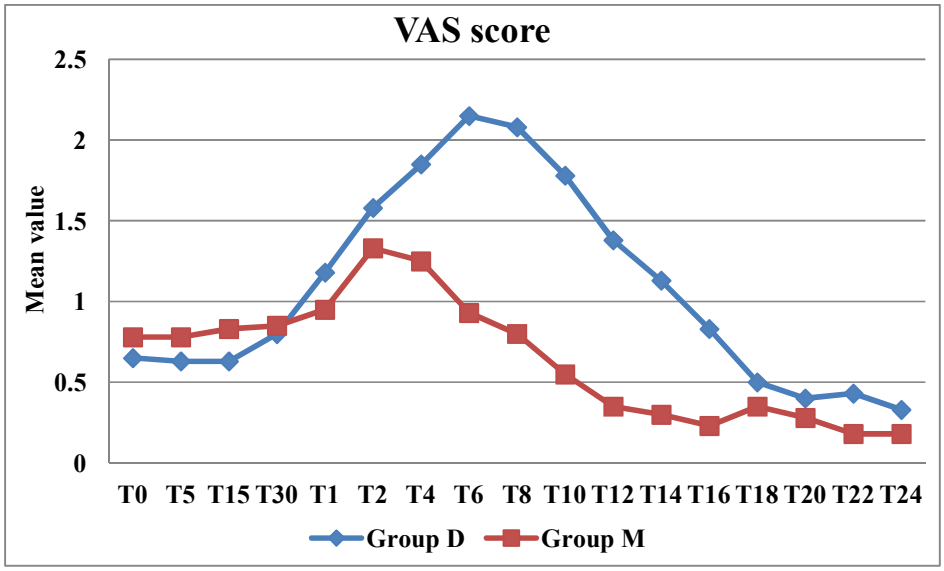

Figure 4: Changes in VAS (pain)

DISCUSSION

Pain, anxiety, agitation and delirium are important causes of morbidity and mortality in critically ill patients, especially those on mechanically ventilation. Proper management of pain and agitation may play an important role in overall patient outcome in the ICU. Patients in the ICU routinely experience pain, both at rest and with routine ICU care and procedures and "analgesia-first sedation" should be used in mechanically ventilated adult ICU patients. Pain should be routinely monitored in all adult ICU patients. Preemptive analgesia and/or non pharmacologic interventions should be administered to alleviate pain in adult ICU patients prior to invasive and potentially painful procedures like chest tube removal.

Adequate and appropriate sedation is essential to avoid the adverse effects of both undersedation and oversedation. Maintaining light levels of sedation in adult ICU patients is associated with improved clinical outcomes: shorter duration of mechanical ventilation and a shorter ICU length of stay (LOS). Maintaining a light sedation with monitoring the depth of sedation using the Richmond Agitation-Sedation Scale (RASS) or the Sedation-Agitation Scale (SAS) is recommended unless clinically contraindicated. Daily sedation interruption or a light target level of sedation has been recommended in mechanically ventilated adult ICU patients.[6] Promoting sleep in the patients by optimizing patients' environment controlling light and noise, clustering patient care activities, and decreasing stimuli at night is recommended.

Dexmedetomidine has been shown to be an effective and safe agent for sedation in mechanically ventilated post-operative patients in ICU patients. In contrast to propofol, it has analgesic effects and in contrast to Morphine, it is not associated with respiratory depression. A short duration of action helps in easy and quick titration of dose as per the patient requirements and has been associated with. It produces a state of cooperative sedation with an easy arousability and helps in early extubation.[7,8]

Patients received the study drugs for 24 hours with the infusion rates adjusted to keep them in the target sedation

score RASS within 0 to -3.

Mean RASS was found to be -2.3 to -0.48 in Dexmedetomidine group and -2.2 to -0.48 in Morphine group across different points of time which was statistically similar. In the MIDEX and PRODEX multicentre studies, Dexmedetomidine treated patients had a higher RASS scores (-1.9 to -0.1 and -1.9 to -0.2 respectively) compared to Midazolam (-2.5 to -0.5) and Propofol (-2.5 to -0.7).[8] In a study by Prerana N Shah et al comparing Dexmedetomidine and Propofol for post-operative sedation, similar sedation scores (Ramsay sedation score) were observed between the groups (2 to 3 in Dexmedetomidine versus 2 to 4 in Morphine).[9]

In our study, incidences of oversedation and undersedation were seen more in patients receiving Morphine with p= 0.0341. Oversedation occurred in 32.5 % of patients receiving Morphine and 12.5% receiving Dexmedetomidine. Similarly, undersedation occurred in 45% patients receiving Morphine and 37.5% patients receiving Dexmedetomidine. The mean duration of targeted sedation was 22.65 ± 1.9 hours in group D and 22.26 ± 1.6 in group M which was statistically similar.

In the DEXCOM study by Shehabi et al comparing Dexmedetomidine with Morphine post cardiac surgery patients, delirium was observed in in 11.7 % patients (Dexmedetomidine 8.6% and morphine 15%).[10] In the MIDEX and PRODEX studies comparing Midazolam and propofol respectively with Dexmedetomidine, incidence of delirium was 7.7% and 2.8 % with Dexmedetomidine versus 7.6% and 6.9 in Midazolam and Propofol respectively.[8] In our study, no patient in either of the groups was observed to develop delirium. This may be due to a shorter study 24 hours versus 5 days in the DEXCOM study and 48 hours in MIDEX and PRODEX. This may also be due to exclusion of patients with renal, neurological and hepatic dysfunction. An adequate sedation levels achieved in our study or underestimation by the observers might have also resulted this. Dexmedetomidine administered for sedation was associated with a lower prevalence of delirium compared to Morphine in DEXCOM study and a review study by Mo Y and Zimmermann AE.[10,11] In many other studies, Benzodiazepines and opioids have been associated with the development of delirium in adult ICU patients.[12-14]

In the DEXCOM study by Shehabi et al, bradycardia was observed more in patients receiving Dexmedetomidine (P < 0.006) but in contrast to our study, hypotension was present more in the Morphine group (P <0.006).[10]

In the study by Venn and Grounds, heart rate was significantly lower in patients receiving Dexmedetomidine than propofol (p= 0.034) without any difference in blood pressure.[15]

As shown in the MIDEX study, Dexmedetomidine had more incidences of hypotension (20.6% versus 11.6%, p =0.007) and bradycardia (14.2% versus 5.2%, p<0.001) when compared to Midazolam.[8] In SEDCOM study, Dexmedetomidine treated patients had more bradycardia (42.2% versus 18.9 %, p <0.001) while incidence of hypotension was similar (56.1% versus 55.7%, p>0.99).[16]

\In our study, pain was adequately managed by supplementation with injection Paracetamol infusions when required. However, patients who received Morphine infusion experienced lesser pain than the patients receiving Dexmedetomidine after four hours of infusions with a mean VAS score of 0.175 to 1.325 and 0.325 to 2.15 respectively (p <0.001 to 0.655).

In the study by Shehabi and co-workers, additional requirements of Morphine for analgesia was comparable in both Dexmedetomidine and Morphine groups.[10]

In the study by Venn et al comparing Propofol and Dexmedetomidine in postoperative mechanically ventilated patients, patients receiving propofol infusions required more alfentanil than patients receiving Dexmedetomidine (2.5 versus 0.8 mg/hr, p=0.004).[15] Similar results were observed by Prerana N Shah and co-workers with a lower VAS score with Dexmedetomidine compared to Propofol (1.78 to 2.48 versus 2.25 to 3.70, p< 0.05).[9]

Dexmedetomidine is associated with significant analgesic actions and supplementation with opioids or non-opioid analgesics can provide adequate analgesia.[6]

There was no significant differences in other parameters including electrocardiogram, haematological or biochemical variables among the groups. Similar findings were observed in studies by Venn et al comparing Dexmedetomidine and Propofol.[15] Dexmedetomidine doesn't appear to have unfavourable effects on renal and liver functions. No other significant adverse effects were noticed with either of the study drugs.

CONCLUSION

We concluded that Dexmedetomidine is better than or at least comparable to Morphine in terms of for providing appropriate and adequate sedation in mechanically ventilated postoperative patients, however the long-term effects of either of the drugs used for this purpose is needed to be assessed.

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