ABSTRACT:

Introduction: This retrospective single centred observational study assessed the safety and efficacy of sedation with Butorphanol and midazolam in critically ill mechanically ventilated patients in an Intensive care unit.

Method: Patients aged between 18 – 80 years admitted to the intensive care unit from July 2018 till December 2018 were included in the study. Medical records were identified by searching the pharmacy database and individual patient medicine cards for the given time period. Patients of the Cardiac care unit were not included in the study.Only those cases where proper documentation of baseline vitals, RASS, CPOT, CAM-ICU score, Age and sex had been documented were included in the study. The regimen consisted of butorphanol (0.48 mg/hour) and midazolam (2 mg/hour). Dose was titrated to achieve optimal sedation and analgesia.

Main outcome measures: Percentage of time within target RASS range. Secondary end points included level of analgesia, prevalence of delirium, adverse event like hypotension, bradycardia, patient self extubation etc.

Result: From this study we can safely conclude that the combination of Butorphanol and midazolam in there recommended doses are quite effective and safe agents for sedation and analgesia in ICU patients on mechanical ventilation.

INTRODUCTION:

Providing sedation and analgesia for Patient comfort is an integral component of bedside care for nearly every patient in the intensive care unit (ICU). For decades, y-aminobutyric acid (GABA) receptor agonists (including propofol and benzodiazepines such as midazolam) have been the most commonly administered sedative drugs for ICU patients worldwide. Practice guidelines for providing sedation in the ICU have identified the need for well-designed randomized trials comparing the effectiveness of different sedative agents for important clinical outcomes.

Butorphanol tartrate is a synthetic parenteral opiate agonist-antagonist. Specifically, Butorphanol is a kappa-receptor agonist and a partial agonist or mixed agonist-antagonist with low intrinsic activity at mu receptor .Because of limited stimulation at the mu-receptor, Butorphanol is believed to produce less respiratory depression and to pose a lower risk of physical dependence than morphine.[2]

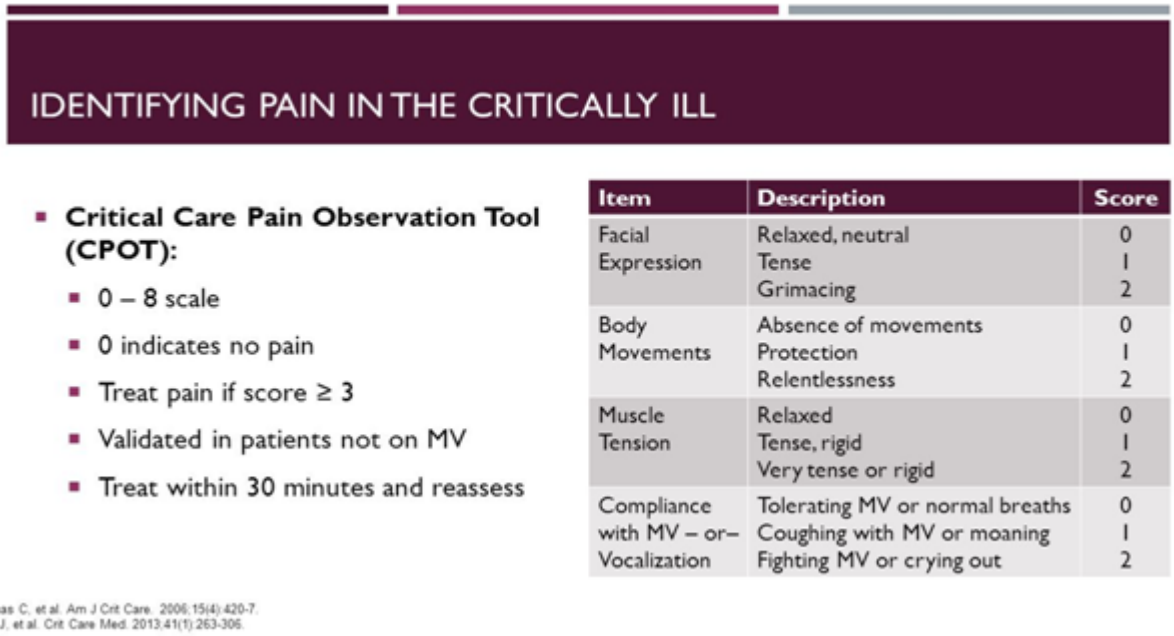
There have been very few studies designed specifically to evaluate the safety and efficacy of Butorphanol for sedation and analgesia in mechanically ventilated patients[3]. Butorphanol with midazolam was being used routinely as sedative and analgesic for mechanicallyventilated patients in the ICU of our institute.Hence we decided to do a retrospective study on 122patients who had received the regimen.

METHODOLOGY:

This was a retrospective observational single centred study. 122 patients aged between 18 – 80 years admitted to the intensive care unit from July 2018 till December 2018 who needed mechanical ventilation were included in the study. Medical records were identified by searching the pharmacy database and individual patient medicine cards for the given time period. Patients of the Cardiac care unit were not included in the study. Only those cases where proper documentation of baseline vitals, RASS, CPOT, CAM-ICU score, Age and sex had been documented were included in the study.

RASS score

Richmond Agitation & Sedation Scale				CAM-ICU
Score	Description			
+4	Combative	Violent, immediate danger to staff		RASS ≥ -2 Proceed to CAM-ICU assessment
+3	Very agitated	Pulls at or removes tubes, aggressive		
+2	Agitated	Frequent non-purposeful movements, fights ventilator		
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous		
0	Alert & calm			
-1	Drowsy	Not fully alert, sustained awakening to voice (eye opening & contact >10 secs)	Voice	
-2	Light sedation	Briefly awakens to voice (eye opening & contact < 10 secs)		
-3	Moderate sedation	Movement or eye-opening to voice (no eye contact)		RASS < -2 STOP Recheck later
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation	Touch	
-5	Un-rousable	No response to voice or physical stimulation		



TREATMENT PROTOCOL:

As per the ICU protocol Inj Butorphanol 6mg (3 ampules) was mixed with 25 mg Midazolam and rest Normal saline to be made a total infusion of 50 ml, was to be started by infusion, where each ml of the solution contained 0.12 mg/ml Butorphanol and 0.5 mg/ml Midazolam. A loading dose of 4ml was to be given followed by maintenance dose of 3.5 to 4 ml/hr. The regimen consisted of butorphanol (0.48 mg/hour) and midazolam (2 mg/hour). Dose was titrated to achieve optimal sedation and analgesia.

Rescue drugs that were allowed were Propofol, other opiods(like fentanyl and morphine) and muscle relaxants.

PATIENT MONITORING:

As per the ICU protocol all patient on mechanical ventilation were monitored closely for signs of agitation and pain using RASS, CPOT, HR, MAP, Respiratory rate. Additionally CAM-ICU score was used to detect presence of residual delirium every 24 hours and the result after 48 hours were included in the study. The nursing records and doctors ICU progress notes were evaluated for incidence of bradycardia, hypotension, allergy-anaphylaxis, during the study period. Other likely adverse events due to inadequate sedation like patient self extubation, vomiting, constipation were also noted from the

nursing notes.

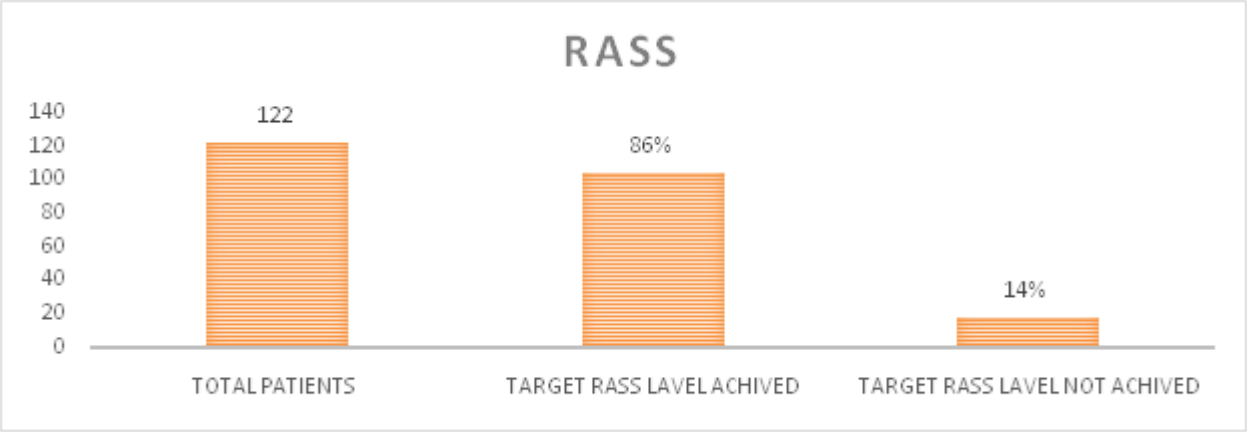
NEUROLOGICAL ASSESSMENT:

As per the ICU protocol daily sedation vacation was done before doing neurological assessment. For this rather than completely stopping the study drug at once, it was protocolized to tapper down the infusion by 2 ml then wait for 10 minutes before doing the neurological assessment, then again tapper down the infusion by 2 ml then wait for 10 minutes before doing the neurological assessment.

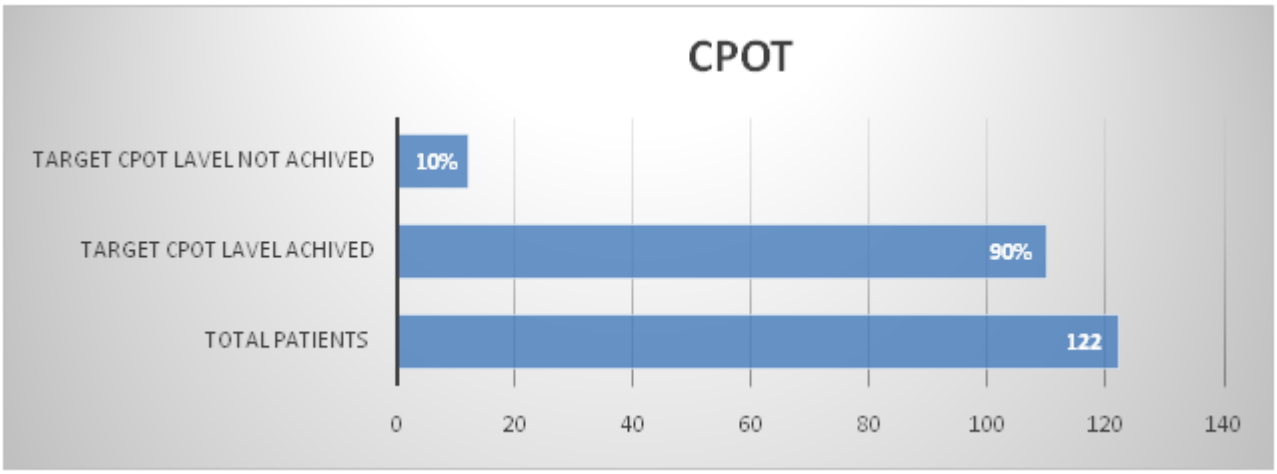
RESULTS:

Target RASS level was achieved in 86% of the patients. Target CPOT level was achieved in 90% of the patients. Around 28% of the patient showed signs of delirium during the study period. Adverse events many included constipation (26%), vomiting (13%), Bradycardia (18%), Hypotension (19.6%). Around 21.3% of the patient required administration of rescue drugs during the study period.

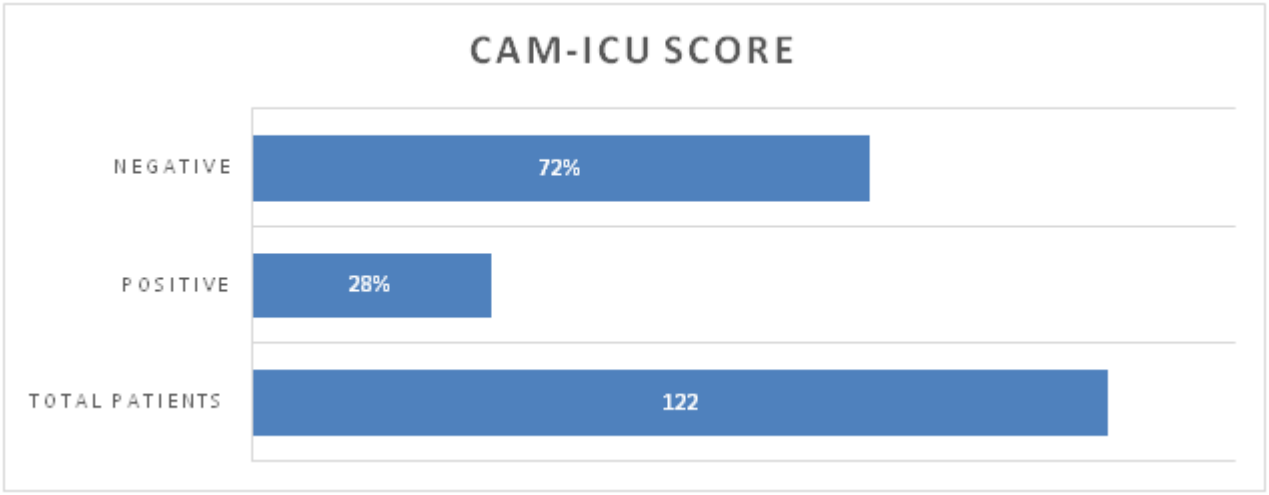
RASS TOTAL PATIENTS	TARGET RASS LEVEL ACHIEVED	TARGET RASS LEVEL NOT ACHIEVED
122	104	18



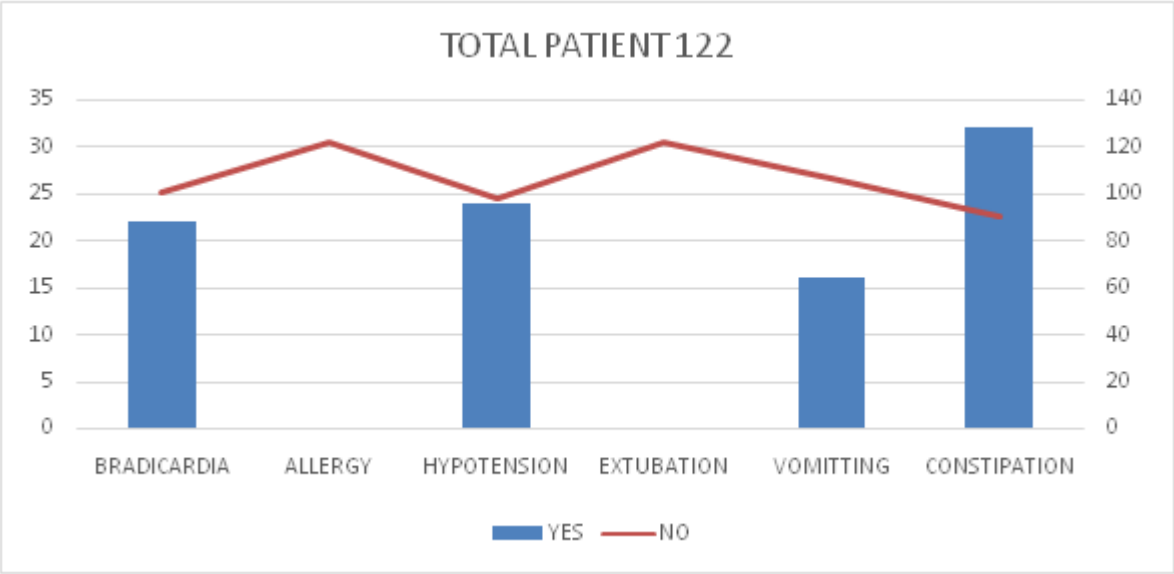
CPOT TOTAL PATIENTS	TARGET CPOT LEVEL ARCHIVED	TARGET CPOT LEVEL NOT ARCHIVED
122	110	12



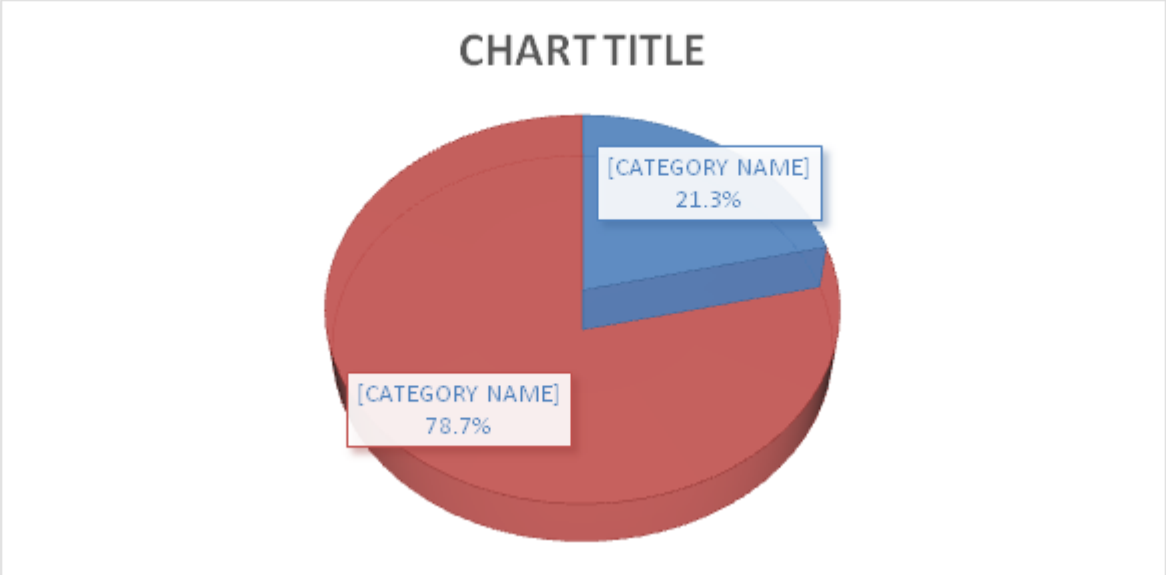
DELIRIUM	TOTAL PATIENTS	POSITIVE	NEGATIVE
	122	34	88



ADVERSE EVENTS	YES	NO
BRADICARDIA	22	100
ALLERGY	0	122
HYPOTENSION	24	98
EXTUBATION	0	122
VOMITING	16	106
CONSTIPATION	32	90



NEEDS FOR RESCUE DRUGS	REQUIRED	NOT REQUIRED
122	26	96



DISCUSSION:

For patients on mechanical ventilation in the ICU, appropriate sedation and analgesia is one of the key factors to ensure patient's comfort and improve the outcome.

Over sedation can lead to prolonged duration of mechanical ventilation /difficulty in

weaning off, longer ICU stay and higher chances of complications. Under sedation can lead to anxiety, hyperactivity of the sympathetic system, delirium etc.

Our study showed that the combination of Butorphanol and Midazolam was quite effective and safe as a sedative and analgesic agent in ICU patients. The target sedation achieved with this combination was comparable with other agents commonly used in ICU like other opiods (fentanyl , morphine), alpha 2 agonist (dexmedetomidate) and GABA receptor agonists (including propofol).

As expected we observed that the incidence of delirium was quite high with this combination.

Additionally it was noted that the prevalence of over sedation was quite high. It seems intensivist preferred to oversedate their patients then undersedate, which might be partly due to fear of adverse events like patient self extubation, airway trauma etc.

CONCLUSION:

From this study we can safely conclude that the combination of Butorphanol and midazolam in there recommended doses are quite effective and safe agents for sedation and analgesia in ICU patients on mechanical ventilation.

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