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ORIGINAL RESEARCH

The association between dexmedetomidine as a single or adjuvant sedative versus other sedatives and the duration of mechanical ventilation and ICU stay in critically ill patients in a central South African ICU

R Swart,[1] G Joubert,[2] G Lamacraft,[1] S Maasdorp[3]

[1] Department of Anaesthesiology, Faculty of Health Sciences, University of the Free State, South Africa
[2] Department of Biostatistics, Faculty of Health Sciences, University of the Free State, South Africa
[3] Department of Critical Care, Faculty of Health Sciences, University of the Free State, South Africa
Corresponding author, email: *reinier.swart@gmail.com*

Background: Sedation is often required in the intensive care unit (ICU) but can be harmful if administered inappropriately or excessively. Dexmedetomidine offers a favourable, cooperative sedation profile, despite a higher relative cost. It also has analgesic and opioid-sparing properties. The multidisciplinary ICU at our central South African hospital adopted the use of dexmedetomidine through the course of 2016. The aim of the study was to determine whether this change in practice affected the ICU length of stay (LOS) and duration of mechanical ventilation at this unit.
Methods: A retrospective cohort analysis of patients' files, who were sedated with midazolam and propofol in 2015 and those sedated with dexmedetomidine in 2017, was conducted. The data gathered included the sedatives used, demographic and vital data, ICU LOS, duration of mechanical ventilation and treatment of side-effects. Group 2015 and Group 2017 were also analysed for possible confounders where appropriate, and these confounders were excluded for a re-analysis. Descriptive statistics were used and results were analysed for range, median, interquartile range (IQR), percentage and frequency. For post-hoc analysis of the effect of confounders, the Spearman rank correlation coefficient was used to determine the association between duration and sedative exposure and either duration of ICU stay or mechanical ventilation. The null hypothesis was set at $p < 0.05$.
Results: Group 2015 comprised 52 patients and Group 2017 60 patients. No difference between the groups was found regarding ICU LOS (median [IQR] 5 [2–14] vs 8.5 [5–12.5] days; $p = 0.10$) or mechanical ventilation (median [IQR] 91 [34–272] vs 129 [58–221] hours; $p = 0.44$). Those who were sedated with dexmedetomidine had better initial prognoses (median APACHE II score 13 vs 18, $p = 0.01$), were sedated for greater fractions of their total ICU stay (median 46% vs 25%, $p < 0.01$), and had a higher incidence of hypotension and bradycardia (36.7% vs 11.4%; $p < 0.01$); which did not relate to a higher mortality. Spearman's rank correlation coefficients also showed a weak to moderate association with longer ICU stay and ventilation duration when the duration of sedation with midazolam or propofol was shorter in relation to ICU stay.
Conclusion: We did not find a reduction in ICU LOS or mechanical ventilation with the advent of dexmedetomidine in our unit. The lack of regular documentation of sedation levels and scheduled sedation breaks might have contributed to these results. Dexmedetomidine has a role to play in the ICU setting, but it should only be used when clearly indicated. Vigilance for hypotension and bradycardia is required when using dexmedetomidine.

Keywords: dexmedetomidine, propofol, midazolam, ICU, intensive care unit, sedation, duration of ventilation, LOS, length of stay

Introduction

The purpose of sedation in the intensive care unit

The most frequent recollection of a patient's intensive care unit (ICU) stay is pain often associated with the accidental removal or disconnection of vital equipment and infusion lines during periods of agitation.[1,2] Patients in pain and discomfort may be agitated, and ameliorating these precipitants could be all that is needed to calm a patient instead of applying pharmacological or mechanical restraints.[3] Sedation in the ICU is commonplace, as shown in Table I. An artificial and stimulating environment, as is commonly found in ICU, can lead to agitation and delirium, the latter being associated with worse morbidity and mortality in up to 27% of mechanically ventilated patients.[4,5]

Sedation practices in the intensive care unit

The term sedation is often interpreted to mean anything from anxiolysis to deep procedural sedation, where patients do not move during deeply painful stimuli, and many sedatives have been developed to this end, as shown in Table II.[6] Consequently, it is important that the desired level of sedation be clearly defined and regular, scheduled sedation breaks be provided.[1,7-9] Subsequently many sedation scales have been developed and more physiologically-based targets have been proposed to monitor sedation in the ICU, such as the use of processed electroencephalography (EEG) monitors.[3,10]

It is important to note that sedation may be harmful when used inappropriately and may, contrary to the healthcare provider's intention, lead to longer ICU stay and mechanical ventilation.[1,3,7,9] The American College of Critical Care Medicine (ACCM) has released the ABCDEF bundle for the assessment, prevention and management of sedation and delirium in the ICU.[11] The ABCDEF bundle encompasses the early treatment of pain, spontaneous awakening and breathing trials, targeting of sedation, detection and treatment of delirium, exercise and family engagement. One has to remember that sedation does not ensure that a patient is pain-free, and analgesia is probably more important than sedation alone in the critical care setting.[12] Many trials have been conducted to determine the superiority of one

sedative over another, and none has yet met this expectation.[13] Most sedatives are also very highly protein-bound and are excreted by the kidneys. Therefore, the interaction between the pharmacokinetics and the pharmacodynamics of a drug should always be borne in mind in critically ill patients with labile biochemistry.[14]

Despite a condemnation of the use of benzodiazepines for sedation in the ICU,[3] their relative haemodynamic stability when compared to propofol, and the significantly lower cost of these drugs compared to dexmedetomidine, give them an advantage in resource-constrained environments. 2,6-diisopropylphenol (propofol) quickly gained popularity as a general anaesthetic and sedative due to its titratability and wide range of effects.[15] It is important to note that, as with any drug, propofol is not without risks, such as hypotension and metabolic acidosis from prolonged use. Dexmedetomidine is often used either as a primary sedative or when others have failed in the ICU, due to the favourable cooperative sedation profile it provides.[3,14,16,17]

Rationale behind the study

The aim of this study was to evaluate whether the introduction of dexmedetomidine at the multidisciplinary ICU at Universitas Academic Hospital in Bloemfontein resulted in a shorter duration of mechanical ventilation or ICU stay to warrant the increase in cost related to its use as shown in Table III. The objectives were to identify the potentially resource-sparing benefits of using dexmedetomidine in Group 2017 (in comparison to midazolam and/or propofol used in Group 2015), by assessing the following parameters:

Primary outcomes:

- duration of mechanical ventilation; and
- ICU length of stay (LOS).

Table I: Indications for sedation in the ICU[1]

Difficulty in oxygenation
Ventilator dyssynchrony (mechanical difficulty in ventilation)
Neuroprotection
Severe pain (e.g. lactrodectism, polytrauma or dressing changes in burns)
Refractory status epilepticus
Severe neuromuscular diseases (e.g. Guillain–Barré)
Agitation or when a patient becomes a danger to him-/herself due to agitation

Secondary outcomes:

- adverse events during sedation (as identified during a retrospective document review), such as hypotensive incidents and bradycardia;
- influence of APACHE II score on primary outcome;
- average sedation times (also as compared to ventilation periods and duration of ICU stay);
- serum creatinine;
- serum albumin (to determine if these values were significantly different); and
- outcome (either death or discharge from ICU).

Methods

This study was designed as a retrospective cohort analysis. The institutional Ethics Committee (UFS-HSD2018/0542/2808) and Free State Department of Health provided ethics approval to conduct the study. A registered professional nurse was appointed to assist in collecting files and file numbers. Drug dispensing registers in the multidisciplinary ICU were used to identify patients recorded to have received propofol or midazolam in 2015, and patients recorded to have received dexmedetomidine in 2017 (convenience sampling). These patients' medical records were collected from the Department of Critical Care at the Universitas Academic Hospital, Bloemfontein. The following information was obtained from their files: age, sex, weight, prescriptions, daily treatment and fluid balance charts, doctors' notes, admission and discharge summary information (including admission and final diagnoses), APACHE II score, creatinine and albumin tests, and heart rate and blood pressure data.

All patients 18 years and older admitted to the multidisciplinary ICU from 1 January 2015 to 31 December 2015 and 1 January 2017 to 31 December 2017, who had been sedated while in the ICU with either dexmedetomidine in 2017, or propofol/midazolam in 2015, were included in the study. Patients had to be identifiable, have prescription and flow charts indicating the sedative, dose, entire duration of sedation and duration of

Table II: Sedatives often used in the ICU[13]

Class	Agents
Hypnotics	Ketamine, propofol, thiopentone
Benzodiazepines	Midazolam
Tranquilisers	Haloperidol
Opioids	Morphine, fentanyl
Alpha 2 agonists	Dexmedetomidine, clonidine

Table III: Cost implications of sedatives versus one day in ICU

Sedative	Cost in ZAR[18,19]	US$ equivalent*
One ampoule of midazolam 5 mg/3 ml	3.69	0.22
One vial of propofol 500 mg/50 ml	46.15	2.73
One vial of dexmedetomidine 200 µg/2 ml	440.33	26.09
One day's stay in ICU (excluding consumables)	10 158.00	601.86

ZAR – South African Rand; US$ – United States Dollar

*Calculated at an exchange rate of 1 ZAR = 16.8930 US$ on 18 March 2020. Information available from: https://www.xe.com/currencyconverter/

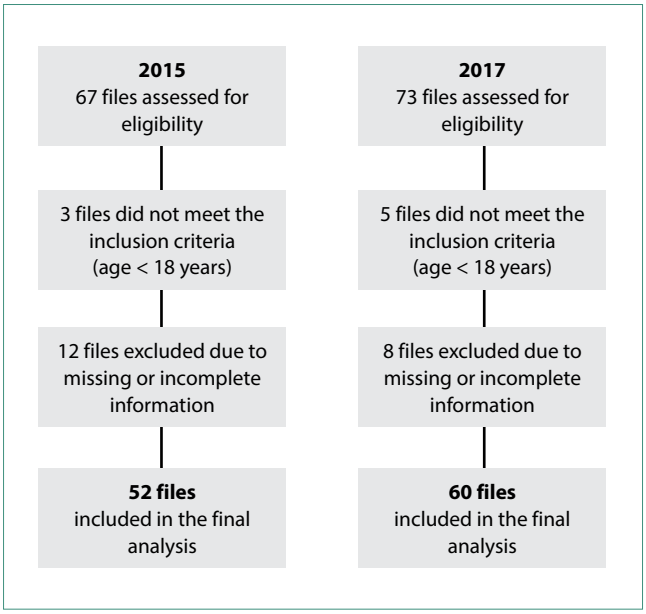

Figure 1: Number of patient files identified and excluded from analysis

ventilation with complete vitals data for the period of sedation. Incomplete or lost patient files were excluded from the study.

The information was entered into an individual data sheet per patient. Calculations were then made to determine the following: total doses of sedatives given during admission, doses of sedatives given per kilogram per hour (maximum and minimum ranges), total hours of sedation and mechanical ventilation, sedation time per hour of admission and sedation time per hour of ventilation. Figure 1 shows the number of files that were included for analysis.

Patients' diagnoses were classified into the following pathological categories (a patient was classified into multiple categories, if appropriate): sepsis, trauma, postoperative, oncology, obstetric, neurosurgical, urology, vascular, general surgery, pulmonology, neurology, cardiology, poisoning, haematology, otorhinolaryngology, plastic surgery, cardiothoracic and rheumatology. After an initial pilot study with four data sheets, it was decided to rather identify any incidences of hypotension and bradycardia as single events, than to collect complete information regarding heart rate and blood pressure ranges and means. The reason for this was that the process to analyse hypotension and bradycardia throughout (retrospectively) could not be representative of the effects of the sedatives only, the data were only recorded hourly (thus significant periods of hypotension or bradycardia could have been missed), and there were too many confounders that could have affected single readings. The institutional definition for hypotension was a systolic blood pressure of less than 90 mmHg or a mean pressure of less than 65 mmHg, while the institutional definition for bradycardia was any heart rate less than 60 beats per minute.

The data were then entered into a single summary sheet for analysis. Analysis was done with the SAS version 9.4 software (SAS Institute Inc.; Cary, NC). All numerical data were found to have skew distributions and were therefore summarised by medians, interquartile ranges and ranges. Categorical variables were summarised by frequencies and percentages. The statistical comparison of the two groups was done by means of the Mann–Whitney test (numerical variables) and chi-squared or Fisher's exact tests (categorical variables); 95% confidence intervals were also calculated for percentage or median differences between the groups regarding primary outcomes.

Spearman's rank correlation coefficients were calculated to ascertain whether sedation time (converted to days), when calculated as a fraction of either ICU LOS (days) or mechanical ventilation time (converted to days), had an influence on the primary outcomes.

The introduction of dexmedetomidine during 2016 was not guided by a protocol, which might have led to a preference in its selection as a sedative drug by some intensivists. This point was introduced during the planning phase of this study and it was decided, for the sake of trying to achieve homogeneity in the two cohorts, to compare the sedative practices of 2015 with those of dexmedetomidine used in 2017.

Results

As shown in Figure 1, the total number of patient files included in the study were 52 for Group 2015 and 60 for Group 2017. The data (Table IV) indicated that during their periods of sedation in ICU, the cohorts were similar, except for the interquartile range of estimated weight (95% CI for median difference Group 2015 – Group 2017 -10; 0) despite medians being the same, APACHE II score (95% CI for median difference Group 2015 – Group 2017 1; 8) and the lower limits of albumin levels (with lower troughs being found in Group 2015, 95% CI for median difference Group 2015 – Group 2017 0; 5).

When examining primary outcomes, it was apparent that the cohorts did not significantly differ in the total duration of ICU LOS (95% CI for median difference Group 2015 – Group 2017 -4; 0) or mechanical ventilation (95% CI for median difference Group 2015 – Group 2017 -54; 24; see Figures 2 and 3). Despite no significant difference in primary outcomes, Group 2015 did receive sedation for a significantly shorter time, as shown in Table V, with 95% CI for median difference Group 2015 – Group 2017 -72; -20.

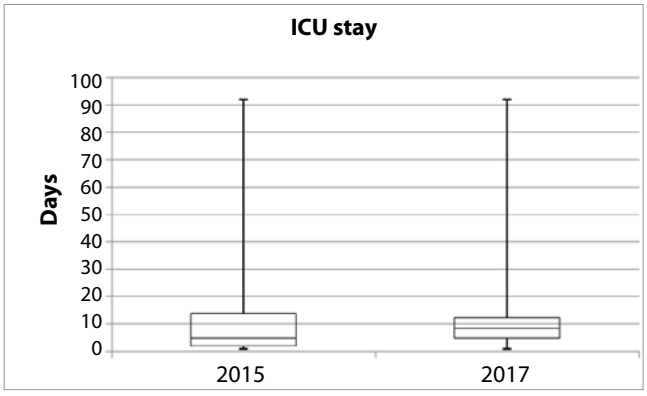

Figure 2: Comparison of length of ICU stay between groups 2015 (n = 52) and 2017 (n = 60)

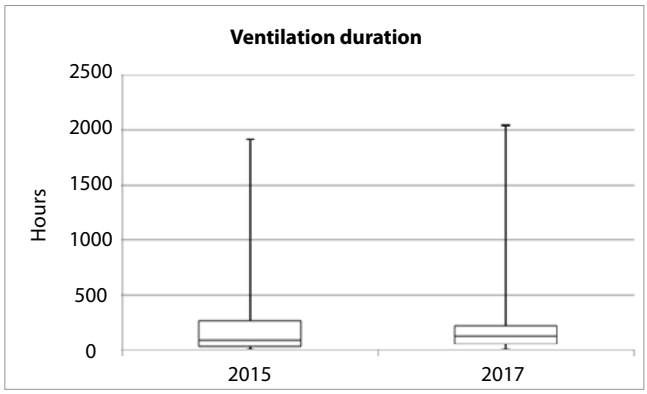

Figure 3: Comparison of duration of ventilation between groups 2015 (n = 52) and 2017 (n = 60)

Analysis of pathological categories showed no statistically significant difference between Group 2015 and Group 2017. However, there was a statistically insignificant trend towards more patients for postoperative stays being admitted in 2015 (11 [21.2%] vs 5 [8.3%]; p = 0.05) and more patients with neurological diagnoses being admitted in 2017 (10 [16.7%] vs 3 [5.8%]; p = 0.07). In order to eliminate the influence of these two pathological categories on the results, the data were re-analysed, with these patients excluded from the cohorts, since postoperative admissions tended to have shorter ICU LOS, and patients with neurological diagnoses, such as Guillain–Barré disease, had longer and more complicated ICU admissions.

The re-analysis demonstrated that after excluding these pathological categories, the duration of ICU stay was significantly longer in Group 2017 compared to Group 2015 (median ICU LOS nine days in Group 2017 vs five days in Group 2015; p = 0.04). However, duration of ventilation remained similar (p = 0.35). The fractions of time that patients were sedated compared to their ICU stay and duration of mechanical ventilation were also significantly higher in 2017 (p < 0.01).

Spearman's rank correlation coefficients for Group 2015 indicated that there was a negative correlation between the fraction of sedation per days admitted and ICU LOS (r = -0.48; p = < 0.01), and between sedation per days ventilated and duration of mechanical ventilation (r = -0.51; p = < 0.01). We did not observe similar findings with the use of dexmedetomidine in 2017. Patients who were discharged alive in Group 2017 (and sedated with dexmedetomidine) were sedated for significantly longer periods of their ventilation time, compared to those who were sedated with propofol or midazolam in Group 2015 (discharged alive, n = 36 [60.0%] vs n = 32 [61.5%], respectively) as can be seen from the fractions of median sedation per ventilation time 0.99 in Group 2017 vs 0.29 in Group 2015 (p = 0.02).

Table IV: Comparison of demographic information and laboratory findings between Group 2015 (n = 52) and Group 2017 (n = 60)

Variable	Group 2015	Group 2017	*p*-value
Male (*n* [%])	29 (55.8)	27 (45.0)	0.26
Female (*n* [%])	23 (44.2)	33 (55.0)	
	Median (interquartile range)	**Median (interquartile range)**	
Age (years)	40 (26–54.5)	32.5 (26.5–51)	0.50
Weight (kg)	70 (60–75)	70 (65–80)	0.04
APACHE II	18 (14.5–24)	13 (8–21)	0.01
Creatinine lower (µmol/L)	57 (43–117.5)	48 (35–92)	0.25
Creatinine upper (µmol/L)	103 (73–216)	106.5 (72.5–213)	0.73
Albumin lower (g/L)	16 (12.5–21.5)	14 (11–17.5)	0.05
Albumin upper (g/L)	22 (16–28)	23 (19.5–27)	0.65

Table V: Primary outcomes and sedation times

Variable	Group 2015 – Median (interquartile range)	Group 2017 – Median (interquartile range)	*p*-value
ICU stay (days)	5 (2–14)	8.50 (5–12.5)	0.10
Sedation time (hours)	33.5 (15–68)	87 (33.5–162)	0.01
Ventilation duration (hours)	91 (34–272)	129 (58–221)	0.44
Sedation per days admitted (fraction)	0.25 (0.13–0.53)	0.46 (0.26–0.72)	< 0.01
Sedation per ventilation time (fraction)	0.43 (0.18–0.82)	0.94 (0.58–1.00)	< 0.01

Table VI: Distribution of APACHE II score and mortality rate per APACHE II strata

Group 2015		Group 2017		*p*-value
APACHE II score	**Mortality *n* (%)**	**APACHE II score**	**Mortality *n* (%)**	
0–19 (n = 27)	7 (25.9)	0–19 (n = 42)	10 (23.8)	0.84
20–29 (n = 15)	6 (40.0)	20–29 (n = 12)	6 (50.0)	0.60
> 30 (n = 6)	4 (66.7)	> 30 (n = 4)	3 (75.0)	1.00
Total (n = 48)*	17 (35.4)	Total (n = 58)*	19 (32.8)	0.97

*Missing data 2015 n = 4; missing data 2017 n = 2.

Patients who were sedated with dexmedetomidine in 2017 had a higher incidence of cardiovascular side-effects, including both bradycardia and hypotension, in comparison to Group 2015 (43.3% vs 11.5%; $p < 0.01$).

When patients were stratified according to APACHE II scores (0–19, 20–29 and > 30), a trend towards longer ICU stay in 2017 in the cohort with APACHE II scores 0–19 (median ICU stay 8.5 vs 5; $p = 0.07$) was observed. Duration of mechanical ventilation was similarly not affected by the APACHE II scores (Table VI). The patients' mortality rates in this study were within the limits of acceptability as predicted by their APACHE II scores,[18] and did not differ between the cohorts (Table VI).

Discussion

This study did not find a reduction in the duration of ICU stay or mechanical ventilation following the introduction of dexmedetomidine for sedation in the multidisciplinary ICU. The current body of evidence supports the finding, except when agitated delirium has been diagnosed or when cooperative sedation is required for other reasons.[19] The results also showed that patients who were sedated with dexmedetomidine while in the ICU in 2017, tended to have better prognoses, based on APACHE II, than those who were sedated with propofol or midazolam in 2015, although being sedated for longer periods of time. When excluding patients with diagnoses that could have confounded these findings (patients who were admitted for postoperative observation or with neurological conditions necessitating ICU admission), an association between dexmedetomidine and longer ICU stay was observed.

The use of dexmedetomidine (especially at higher ratios to duration of admission or ventilation – likely due to the more favourable sedation profile clinically) was associated with a higher incidence of side-effects, which, however, did not seem to affect mortality. This finding was in keeping with Mirski et al.,who showed that the use of dexmedetomidine was associated with more incidents of bradycardia.[20] This reinforces the point that the choice of sedative for the individual patient and how it is administered, are likely more important to the outcomes of the patient than habitual preference of one drug over another.[21] The finding that patients who were discharged alive in Group 2017 with higher ratios of sedation per ventilation time is also contrary to current literature.[15]

Reade et al. showed a 17.3 hour improvement in mean ventilator-free time at seven days when dexmedetomidine was used in agitated delirium.[19] Due to this evidence, it was postulated by Shehabi et al. that dexmedetomidine would perform superiorly when compared head-to-head with other sedatives in a randomised controlled trial, although the SPICE III trial did not substantiate this perception.[15] Dexmedetomidine has been shown to have benefits over midazolam with regard to mechanical ventilation, but at the risk of added cardiovascular side-effects.[19,22]

Propofol is a potent vasodilator with negative inotropic and chronotropic effects. It is also associated with propofol-related infusion syndrome.[3,14] It has been reported that dexmedetomidine is not inferior to propofol with regard to the incidence of delirium, duration of mechanical ventilation and length of ICU stay.[22,23]

The Intensive Care Society of the United Kingdom recommended non-benzodiazepine over benzodiazepine sedation strategies, but this recommendation has not permeated to all units.[3] Previous randomised controlled trials showed that midazolam was associated with both a higher incidence and longer duration of delirium when compared to dexmedetomidine.[22-24] Zaal et al. found that the deliriogenic effects of midazolam were dose-dependent and more prevalent with continuous infusions.[25] Lorazepam has not escaped this scrutiny, with the MENDS study showing that the use of dexmedetomidine was associated with more delirium-free and coma-free days in ICU.[26] When compared to midazolam, propofol has been shown to reach sedation targets earlier, with faster recovery after cessation of the infusions.[27]

A recent randomised controlled trial failed to show that the use of typical or atypical antipsychotics was superior to placebo in reducing the duration of either hyperactive or hypoactive delirium.[10] The use of benzodiazepines is not supported by recent guidelines in sedation or the management of delirium.[28]

Early deep sedation has been shown to result in longer times to extubation and higher 180-day mortality rates.[16] One randomised controlled trial indicated that lighter levels of sedation were associated with shorter ICU stay and duration of mechanical ventilation versus deeper sedation.[29]

Although there was no statistically significant difference in the primary outcomes between prognostic strata, a trend to longer ICU stay and the use of dexmedetomidine in the APACHE II 0–19 group is counterintuitive to what most critical care practitioners would hope to achieve for seemingly healthier individuals.

Strøm et al. first described the benefits of analgosedation in 2010.[30] They found that the use of morphine alone (compared to a combination of morphine and sedation) reduced ventilated days, which reinforced the stance that effective analgesia alone might obviate the need for pure sedatives.[12] This study supported the use of analgesia in ICU and contributes to the rationale behind the motivation for adequate analgesia in the current guidelines. The analgesic properties of dexmedetomidine and lower opioid requirements associated with its use, might also have led to the belief that it would perform superiorly according to the principles of analgosedation.[14]

The ABCDEF bundle for critical care has been validated by Pun et al. in over 15 000 patients, to reduce the incidence of death within the first seven days, next-day mechanical ventilation, coma, delirium, physical restraint use, ICU re-admission, and discharge to a facility other than home.[31] Therefore, this bundle should receive strong consideration for implementation in units such as ours.

The negative Spearman's rank correlation coefficients for sedation per days admitted compared to ICU LOS, and sedation per days admitted compared to duration of ventilation in the 2015 group, indicated a weak to moderate association of sedation with longer ICU LOS and ventilation hours. The association was observed when less sedation was given with propofol and/or midazolam per period of time in ICU. This finding was contrary to current literature indicating that longer sedation times lead to longer ICU stay and increased morbidity.[32]

Limitations

The study design was retrospective in nature and due to uncontrolled confounders, causality was difficult to determine. The sample size was limited and might have affected the determination of statistical significance. Vital signs were only recorded every hour and episodes of hypotension and/or bradycardia might have been missed. Selection bias could have played a role in the sedation practices in 2017, as propofol and midazolam were in use during that year, although analysis did not show a statistically significant difference in pathological categories. Patients' weights were often estimated by their attending physicians, which could have also influenced calculations regarding the weight-indexed doses of sedatives. Sedation targets were not documented, if used, and the lack of scheduled sedation breaks might also have influenced the duration of mechanical ventilation, ICU LOS and final outcomes.[8,9]

The implementation period regarding the use of dexmedetomidine in 2016 might have played a substantial role in the decision as to which drug to use to sedate any particular patient by a given intensivist during the 2016–2017 period. This trend could have continued into 2017, but it was difficult to analyse retrospectively, as the decision on which drug to use was neither part of the standard protocol in our unit, nor was the reason for using individual sedatives routinely recorded.

The arbitrary limits that were defined for hypotension and bradycardia are controversial, but for the sake of uniformity limits had to be defined.[33] While the APACHE II score as a physiologically-based prognostic score has its limitations, and has largely been replaced by newer scoring instruments, its simplicity and ease of use make it a regularly used tool in our unit.[34]

Conclusion

This study did not show a reduction in ICU LOS or mechanical ventilation with the advent of dexmedetomidine in our unit. We did, however, find a significant association with longer time of sedation per time admitted with the use of dexmedetomidine in 2017, compared to propofol and/or midazolam in 2015. Post hoc analysis also showed longer ICU LOS in Group 2017 (despite significantly lower trough albumin levels) when patients with postoperative admissions and neurological diagnoses were excluded in both groups. This finding was contrary to the belief that introducing the use of dexmedetomidine more regularly in our unit would lead to shorter ICU LOS and mechanical ventilation. There was also a significantly higher incidence of side-effects with the use of dexmedetomidine, although mortality was unaffected. It should be noted that dexmedetomidine has a definite place in the management of the critically ill patient. Sedation in the ICU (with any drug) should be (i) indicated, (ii) targeted and (iii) withdrawn or interrupted, where appropriate. Therefore, based on our results, we recommend that sedation be practised as outlined in the Society of Critical Care Medicine's Clinical Practice Guideline for the Prevention and Management of Pain, Agitation and Delirium.[10]

The findings of this study, despite its appreciable limitations and retrospective nature, should by no means serve to preclude the use of dexmedetomidine in the critical care setting. It should rather serve as a warning against the indiscriminate use of dexmedetomidine sedation in the ICU.[3,10] In developing countries, where resources are sparse, newer and more expensive drugs should be used as alternatives to cheaper sedatives only where its higher cost could potentially be offset in other areas. More prospective research is needed in this area in developing countries to determine whether the appropriate use of dexmedetomidine may be linked with such benefits.

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

The institutional Ethics Committee (UFS-HSD2018/0542/2808) and Free State Department of Health provided ethics approval to conduct the study.

ORCID

R Swart https://orcid.org/0000-0003-3873-4424
G Joubert https://orcid.org/0000-0002-3728-6925
G Lamacraft https://orcid.org/0000-0002-3744-6204
S Maasdorp https://orcid.org/0000-0003-4553-0518

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