Advanced Nursing & Patient Care International Journal
ISSN: 2642-0147

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Research Article *Volume 4 Issue 2*

Impact of Sedation Dosing, Hepatic and Renal Dysfunction on patient outcome in Intensive Care: A Retrospective Pilot Study

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Received Date: November 22, 2021; **Published Date:** December 28, 2021

Abstract

Introduction: Sedation management with hepatic and renal dysfunction have been associated with negative outcomes in critically ill ICU patients. This study examines the impact of sedation practices and management; and hepatic and renal function data on critically ill patients' short and long-term outcomes.

Methods: Sedation dosing, hepatic and renal function data were collected from ICU flow charts of 33 patients who had been admitted to ICU and sedated for up to five days between 1st July 2015 and 31st July 2016. The five-day period provided adequate time to establish management of sedation, hepatic and renal function data in relation to patient outcome. Invitation to participate in an open-ended interview, consent forms including the Hospital Anxiety and Depression Scale (HADS) with self-addressed envelopes were sent to all 33 participants 36 months post ICU discharge.

Results: Ten (n=10) participants completed the Hospital Anxiety and Depression Scale (HADS) and two participants were interviewed 36 months post ICU.

Patients with high sedation dosing, elevated hepatic and renal function data had a longer ventilator, ICU and hospital length of stay (LOS) and high HADS scores. The only patient who was interviewed, reported poor functional capacity and cognitive decline. His wife reported changed lived experience in which she longed for her pre ICU husband to return.

Conclusion: Sedation dosing; hepatic and renal dysfunction are associated with negative short and long-term outcomes for ICU patients.

Keywords: Intensive care; Sedation Scale; Sedation monitoring; Anxiety; Depression; Anxiety and depression score; Hepatic function; Renal function

Introduction

Sedation is integral in the management of critically ill patients in intensive care units (ICUs) [1-3]. Sedation has been examined extensively in Australia and globally [2-5] with fentanyl and morphine; midazolam and propofol as commonly used analgesic (opioid and sedative) agents [6-8]. Despite this, sedation and analgesic management remains problematic with ICU length of stay (LoS) correlating with high opioid and sedative administration [3]. Though it

should be noted that the use of sedation scales has had some positive effect with the Richmond Agitation Sedation Scale and the Riker Agitation Sedation Scale being the mostly used in Australian ICUs. Additionally, Nurse Consultants play an integral role in the facilitation of proper sedation and opioid management [5]. Fundamentally, the major problem with sedation and analgesia is finding the balance – keeping the patient in the corridor window without adverse effects. The risks associated with suboptimal sedation management i.e. as self extubations; endotracheal tube (ETT) malpositioning from patients pulling on them; desaturations resulting from patients biting on the ETT; excessive agitation requiring restraint use; increased ICP exceeding desired limits; delayed extubations due to patient over drowsiness are well documented [1,8,9] (i.e. self extubations; ETT malpositioning from patients pulling on them; desaturations resulting from patients biting on the ETT; excessive agitation requiring restraint use; increased ICP exceeding desired limits; delayed extubations). Additionally, hepatic and renal dysfunction have been known to impact pharmacokinetics of sedation and analgesic agents used in Critically ill patients in ICU [10].

This single centre retrospective pilot study examines the impact of sedation dosing and dysfunctional hepatic and renal function on patients' short- and long-term outcomes.

Aim

The aim of this study was to examine the impact of sedation dosing and hepatic and renal dysfunction on short- and long-term outcomes of critically ill patients.

Study Questions

Is sedation dosing related to short and long-term outcomes of ICU patients?
Does hepatic and renal dysfunction impact on patient short/long-term outcomes in sedated mechanically ventilated patients?

Ethics

Ethics approval was obtained from the ethics committee of the research governance committee on 28th June 2016 (Ethics reference number 16/06/15/5.09).

Methods

A retrospective pilot study. Initially a multicentre mixed method design was going to be utilised to conduct the study. However, one hospital was not included due to inability to provide all the requested data. Additionally, due to poor response, the qualitative aspect of the study was not reported included in the analysis and discussion. For the quantitative part, a retrospective clinical audit of 33 medical records out of 1004 of mechanically ventilated patients admitted to XXX teaching hospital ICU over a 12-month period was undertaken at 36 months post ICU discharge. The ICU is general catering for both adults and paediatrics with conditions ranging from general medical and surgical, cardiac and neurosurgery. Ninety percent of nurses are ICU trained with intensivists, ICU fellows and Senior Registered Medical officers. The ICU has been expanded to cater for the ever-increasing catchment area as it operates retrieval service besides telehealth from rural areas in the Region. A sedation tool was used to collect sedation scoring, titration and hepatic and renal function data from the time of intubation up to five days following. The Hospital anxiety and depression Score (HADS) [11] was sent out to the cohort at the end of quantitative data collection. The potential participants were verified to be alive by looking through the medical records and contacting family members before the invitations to participate, consent forms and HADS were sent out.

Research Questions

Is sedation management related to short and long-tern outcomes of ICU patients?
Is patient hepatic and renal function status related to patient short/long-term outcomes in sedated mechanically ventilated patients?

Objectives

This pilot study examines the impact of sedation dosing and hepatic and renal dysfunction on short- and long-term outcomes of critically ill patients.

Participants

Thirty-three (n=33) charts of patients who were admitted to xxx ICU between 1st July 2015 and 31st July 2016 who fulfilled the criteria were purposively audited. Data the Excel spread sheet was examined for patients with up to five days of ventilator days. Being a pilot study, 33 (n=33) charts were identified, 200 were excluded as the patients were deceased and 785 were purposively excluded as predetermined number was reached. Patient information and consent forms including the HADS questionnaire were sent to all 33 participants 36 months post ICU discharge. Only ten (n=10) returned HADS Scores and six (n=6) returned consent forms. Only one (n=1) couple were eventually interviewed and five (n=5) withdrew their consent to be interviewed.

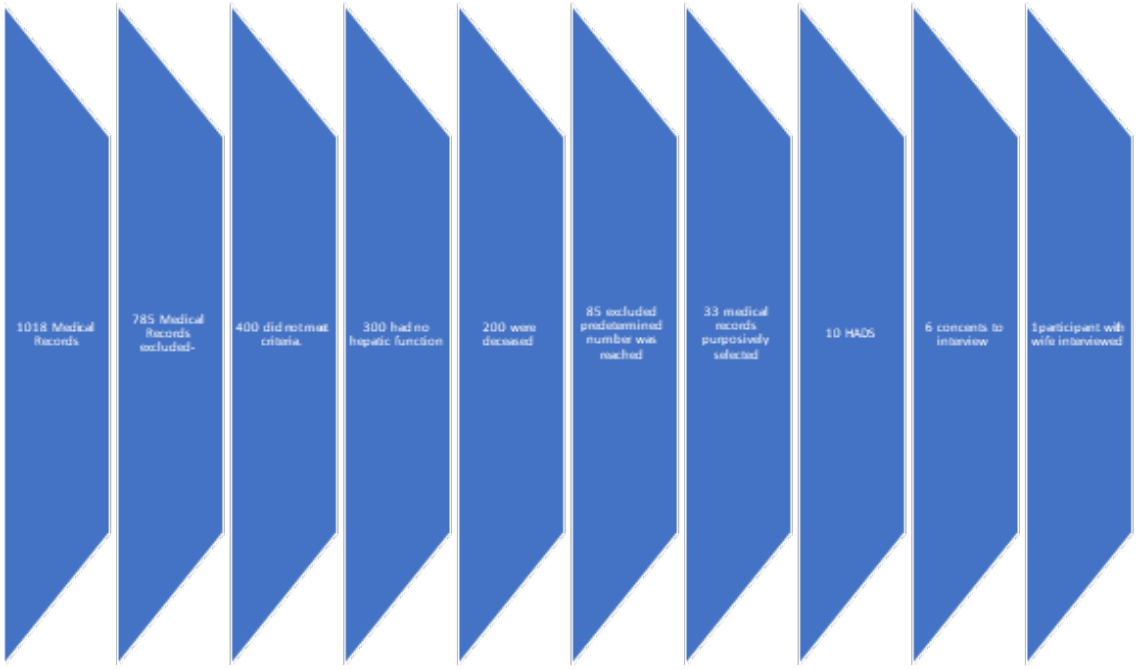

Figure 1: Recruitment process.

Inclusion criteria

Charts of patients who were:

Admitted to ICU between 1st July 2015 and 31st July 2016

Aged 18 years and above at the time of admission to ICU

Required mechanical ventilation for up to five days after intubation

Exclusion criteria

Patients:

Whose medical records were missing.

Medical Records identified after purposive sampling was done.

Medical records of deceased patients.

Data Collection

Data collection was conducted by one researcher with knowledge about sedation assessment and management through the Health Information System of the hospital using a Sedation Audit Tool. Homogenous purposive sampling was conducted. Inter-rater reliability was achieved by another researcher randomly and independently checking at least ten medical records during the data collection period. The Sedation Audit tool devised by Manias, et al. [9] was modified by adding weight, height, serum creatinine, liver function tests (Alanine Aminotransferase and Aspartate Aminotransferase and Gamma Glutamyl Transferase), partial arterial oxygen and carbon dioxide levels from arterial blood gases to the tool before being utilised in this study. Information sought was on: patient demographics; progress notes written about sedation and analgesic medications used for management of sedation; reversal agents used; frequency of monitoring; sedation scoring systems to assess sedation levels; use of intensive care protocols for sedation; sedation scores obtained and times of scoring; goals of sedation management; use of sedation scoring systems; utilisation of objective measures for assessing sedation such as neurological monitoring equipment. In addition, information about whether changes to sedation goals were made and reasons for doing so was collected.

The Sedation Audit tool was based on the sedation scoring system tools such as the Richmond Agitation Sedation Scale (RASS), Glasgow Coma Scale (GCS); Modified GCS and the Vancouver Sedative Recovery Scale (VSRS). For the ICU setting under study, we added the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), Critical Pain Observation Tool (CPOT) and the Faces of Pain Scale. However, they were not documented as part of sedation/pain scoring/assessment. All these were added to the tool for optimal auditing and determination of frequency of utilisation of scoring tools.

For objective measures, tools such as the continuous electro-encephalography (EEG); Bispectral index (BIS), actigraphy (movement monitor), audible evoked potentials (AEP); and somato-sensory evoked potentials (SSEP) were included to determine if goal directed sedation protocols were used. However, they were not part of the documentation in the particular ICU setting.

From Manias, et al. [9] work, the Sedation Audit tool was tested by five independent sedation experts namely an intensivist, ICU pharmacist, ICU fellow, ICU nurse educator including an ICU nurse by completing the content validity tool [12] for clarity, representativeness and comprehensiveness. Data on long-term outcomes was collected by surveying survivors of ICU using the HADS and interviews 36 months after ICU discharge.

Data Analysis

Data were initially collected on a hard copy of the data collection tool and then transferred onto a Microsoft (MS) Excel File (version 2010). Data was then transferred to JMP software for statistical analysis by a statistician. Qualitative data was not analysed as the sample was too small to generate generalizable results. An Excel spread sheet was used to manage descriptive data which was then used as tables and charts to provide a clear picture of sedation dosing, hepatic and renal function including demographic data.

Results

The mean age was 64.5. There were more males (n= 24) than females (n=9). There were more medical general ICU patients than surgical as demonstrated in the table below.

Participant	Age	Gender	Reason for Hospital Admission	Reason for ICU Admission	Past Medical History
1	71	M	Subdural haemorrhage	Sedation and control of ICP	High BMI HTN DM MI IHD GORD Upper GIH Deodenal and gastric ulcers hearing impaired Glaucoma peripheral neuropathy extensive psoriasis
2	65	M	PEA Bronchospasms	MV- management of acidosis	HTN COPD Smoker (65 pack for years) intracranial aneurysms-SAH grade II clipping MCA + RMCA obesity hypercholesterolaemia
3	70	M	Status Epilepticus Metabolic Acidosis L) Frontal Neoplasm	cardiogenic shock Marked metabolic acidosis	Hypertension Hypercholesterolaemia
4	70	M	CABG x 3	Post op CABGs monitoring inotropes	Ex-smoker HTN T2DM CCF EF 20% CAD Ischaemic cardiomyopathy Appendectomy
5	75	M	CABGS Redo AVR	Monitoring	GORD AVR 2005 Aortic incompetence Dyspnoea on exertion+ fatigue Redo- pericardial bleed (returned to theatre) Radical prostatectomy Hypercholesterolaemia Thrombocytopaenia Peripheral Neuropathy Ex-smoker Obesity Vertigo
6	42	M	Myocardial Infarction	CABGS X 4 monitoring	CAD Smoker HTN Hyperlipidaemia Appendicectomy R) knee washout
7	65	F	Seizures + Anaemia	seizure control, Monitoring, airway maintenance	Non epileptiform seizures, Abnormal EEG Asthma , Developmental delay, Previous MVA - wheelchair bound, VRE Migraines
8	80	M	VF arrest	Ongoing shock, inotropes, monitoring, IABP	HTN, Hyperlipidaemia, CVA 2014, Bilateral Carotid stenosis 50%, PVD
9	64	M	Small bowel obstruction, Sepsis, Pneumonia	Respiratory distress, reduced LOC	IHD, CABGs X 3, Severe COPD - asbestos exposure, Ex-smoker, HTN, chronic back pain, Bipolar disorder, Previous bowel perforation - Hartmans, Schizophrenia

10	77	M	AAA repair	vasopressor support, monitoring	AAA, HTN, Ulcerative Colitis, Hypothyroidism
11	78	M	Cardiac arrest	PEA, Monitoring	AF, PPM, AV block/slow AF, Cardiac arrest, Pulmonary HTN, Diabetes mellitus, CKD
12	66	F	Small bowel obstruction	Sepsis, Monitoring	Anxiety, Depression, Pseudo seizures, Dyslipidaemia, GORD, Insomnia, Hysterectomy, Oophorectomy, Appendicectomy, Laparotomies 2008;2016
13	67	M	Fall, rib fracture, pneumothorax, influenza, upper GIH, laparotomy, deodenotomy,	Monitoring - inotropes, mechanical ventilation	COPD, Ex-smoker - 40 pack, stopped in 2014, Pneumococcal pneumonia, ICU admission in 2014, Prostate Cancer, ETOH 8/Day
14	60	F	APO, Cardiac failure (congestive)	monitoring, inotropes	ESRD - Haemodialysis, GORD, HTN, CAD, Previous APO 20 NSTEMI, Hypercalcaemia arrest 2012, Depression, Ex-smoker
15	51	M	DSP Carbamazepine, paracetamol and Ethanol	Monitoring	Severe depression, Generalised Stroke Disorder, Previous episodes of DSP
16	62	F	Intraventricular haemorrhage, obstructive hydrocephalus, raised ICP	subarachnoid haemorrhage	Coeliac disease, Hysterectomy, asthma, Neuropathic pain
17	64	M	OOHCA - STEMI	Cardiogenic shock, APO - MV + Monitoring	Pleural plaques - asbestos exposure, Hyperlipidaemia, Hypertension, Rhinoplasty
18	91	M	Low MVA >5 # ribs	Depressed LOC	COPD, HTN, Prostate Cancer, CRF baseline GFR 35
19	69	F	MVA multiple # c2, pelvic, radius	monitoring, inotropes	IHD, High Cholesterol, CRF, anxiety
20	87	M	Upper airway obstruction	airway management, Monitoring, Inotropes	IHD, CABGS X5 + Stents, Unstable angina, Sick sinus syndrome - PPM, Type 2 diabetes mellitus, Hypertension, Benign prostate hypertrophy, Hypercholerosterolaemia, Recurrent melanomas
21	32	M	Amphetamine toxicity leading to sympathomimetic syndrome, overdose and multi organ failure, seizures	airway maintenance, monitoring	?HTN, Previous OD GHB 2015, recreational drug use
22	66	M	Low GCS, Low BP, Hypothermia, tachycardia and tachypnoea	Decreased GCS requiring intubation	Parkinson's disease, Solar Keratosis, T8 wedge #
23	51	F	Hypotension, acidosis, confusion, sepsis	inotropes, monitoring	T2 DM - peripheral neuropathy, Bipolar, Pancreatitis, chronic back pain

24	68	M	Traumatic Brain injury	Monitoring post craniotomy	CVABG, Hypertension, Hyperlipidaemia, Type diabetes mellitus
25	72	F	MV Replacement (tissue)+cryoablation + excision of atrial appendage	Monitoring, inotropes, mechanical ventilation	AF, CCF, COPD
26	54	F	Ischaemic stroke, MVR	Monitoring, Inotropes	Type 2 diabetes, Rheumatic fever, Heterozygous fenter V Leiden, Depression, Chronic back pain, CIN3 Ex, Smoker
27	67	M	multiple trauma and splenic laceration	inotropes, monitoring	HTN, Asthma/COPD, obesity, arthritis, chronic pain
28	49	M	RAF Cardiogenic Shock	vasopressors and monitoring	x2 recent chest infections
29	56	M	Shoulder arthroscopy + acromyoplasty	Monitoring	OSA, Gout, Obesity, Dyslipidaemia
30	53	M	Grade IV subcardia haemorrhage	inotropes/ vasopressors, mechanical ventilation	asthma, smoker, heavy ETOH
31	86	M	Sepsis	Inotropic support	CAP, IHD, PPM, HTN, T2DM, Appendectomy,/cholecystectomy, GORD, Bilateral TKR, Gout, TIA, Restless legs, CKD
32	54	M	intracranial haemorrhage	ICP monitoring, mechanical ventilation	HTN, chronic back pain, disc bulge? Which one?, on NSAIDS, cortisone injections, panadeine forte, Heavy ETOH use, caretral aneurysims - chipped RS ICA, RS MCA
33	40	F	T2 RF 20 Severe community acquired pneumonia	Inotropes/ Vasopressors	Syringonyelia - cenncothoracic syninx leading to myelopathy, posteriro roass + C1 decompression, Synangopleural shant connected to syringo peltiald shant 2014, worsening myecopathy, depression, OSA - CPAP, Psoriasis, mild cognitive impairment, osteoporosis
Average	64.3				

Table 1: Participant Demographic, Admission and Past Medical History Data

Practices and Management of Sedation Management

The study shows that the most frequently used sedative was midazolam, followed by propofol. Dexmedetomidine was less frequently used. The most frequently used analgesic infusion was morphine followed by fentanyl.

The average dosing of sedatives appeared reasonable. There was demonstration of sedation interruption in some instances. Sedation bolusing was conducted for agitation and preprocedural. However, sedation dosing was related to longer ventilator, ICU and hospital LOS. Five (n=5) of the cohort with long ICU LOS had reasonable doses of fentanyl and propofol. These participants were all males aged between 65 and 76 years.

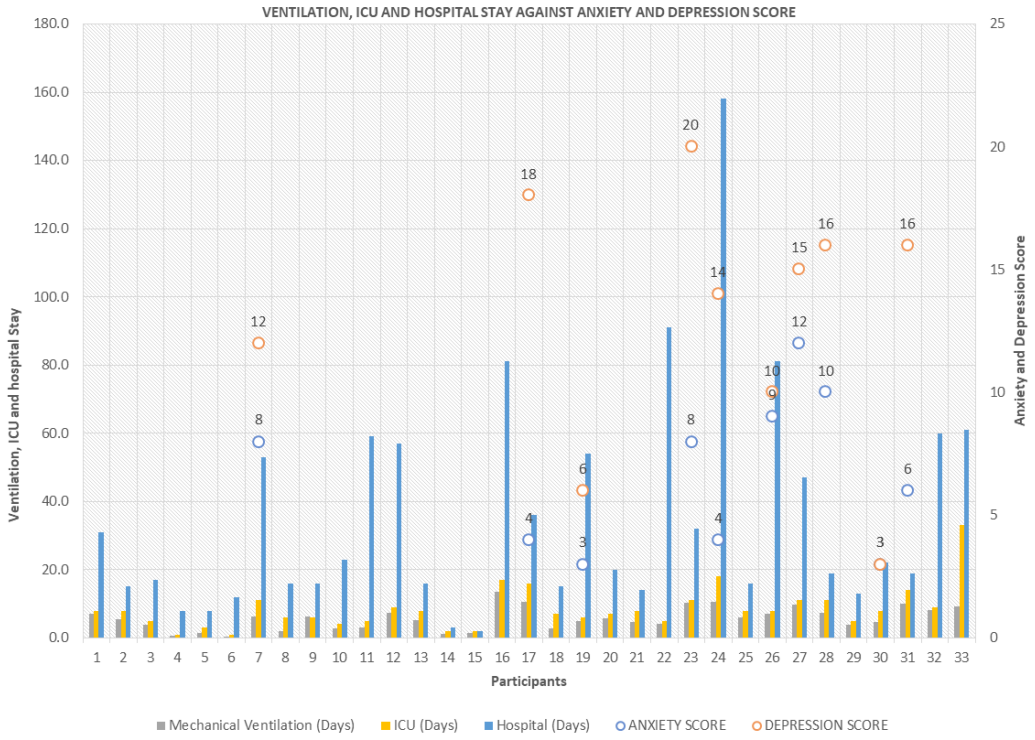

Figure 2: Sedation and analgesic agents Compared to patient Ventilator, ICU and Hospital LOS including HADS Scores

Sedation Management Related to high anxiety and depression scores of ICU Patients

Patients with a higher total dose of sedatives also scored highly on the HADS questionnaire.

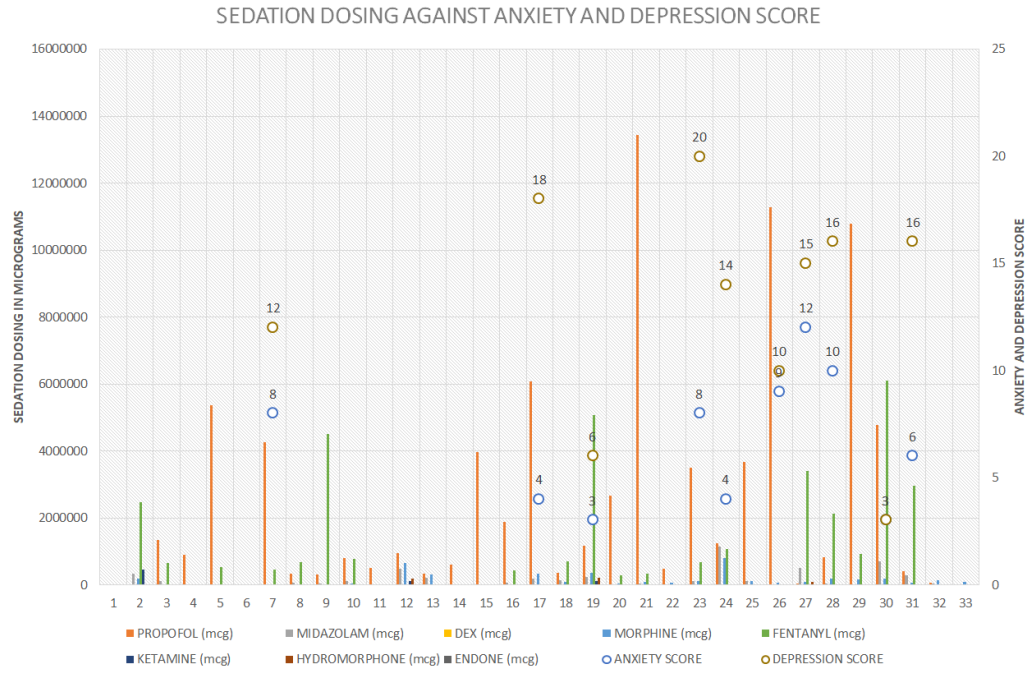

Figure 3: Showing sedation dosing data with HADS scores.

Nine (n=9) participants had an ICU LOS greater than 10 days demonstrating a relationship between elevated hepatic and renal function data and ICU LOS. Long-term outcomes were difficult to assess as only ten (n=10) participants filled in the HADS. Interestingly, Depression scores were generally higher than anxiety scores. The lowest anxiety score was three and the highest was twelve. Depression scores ranged from three (n=3) to twenty (n=20). Eight (n=8) had high depression scores 10-20, one (n=1) participant scored 3 and another scored six (6). Participants with lower scores (n=2) had a short ICU LOS and normal hepatic and renal function data. It is also notable that participants with high HADS scores had no history anxiety or depression.

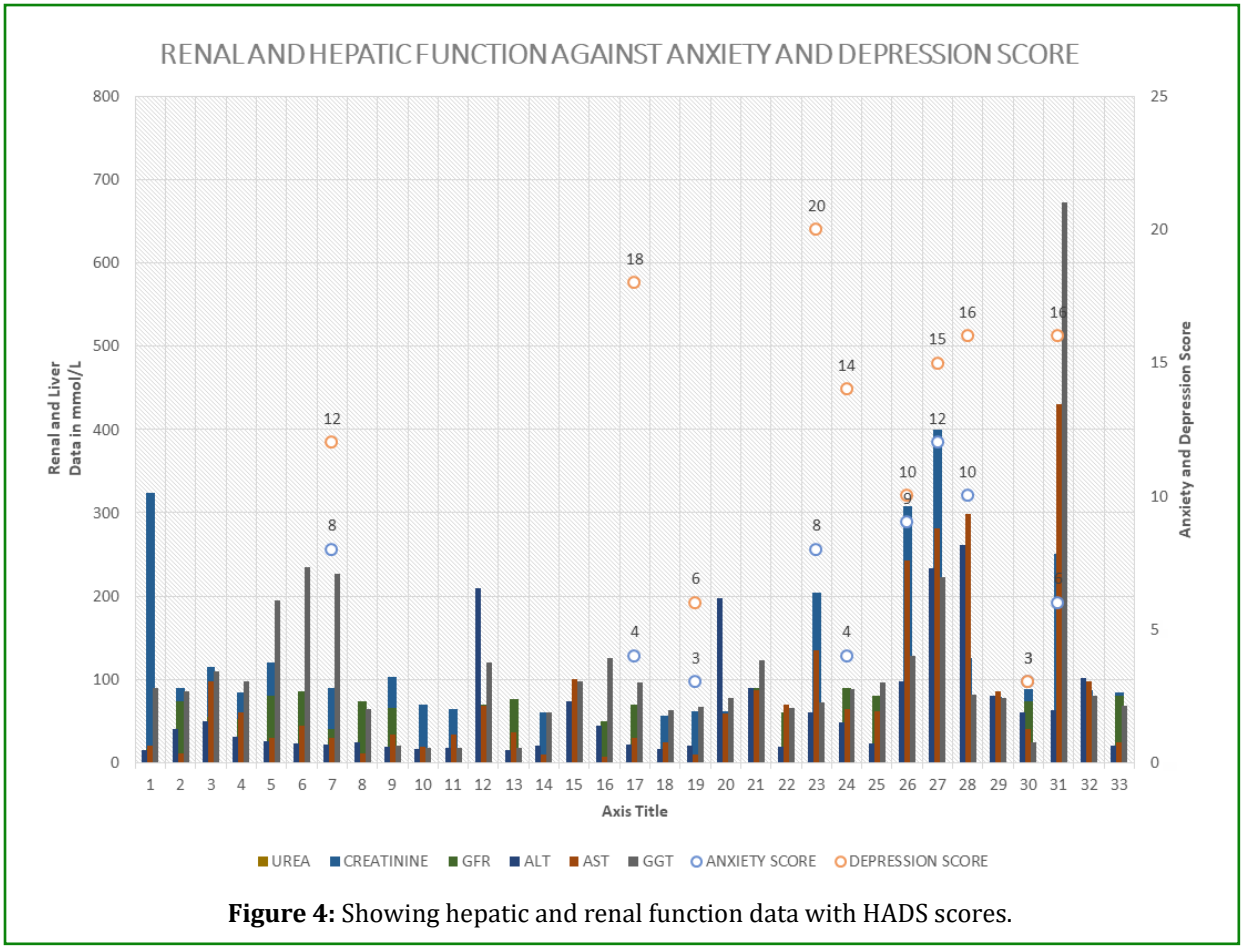

Figure 4: Showing hepatic and renal function data with HADS scores.

Qualitative Data

Despite only one couple having completed the interview: the husband aged 71 and the wife aged 68, the fndings are disseminated to validate their experience. This couple was interviewed together in one setting. Three major themes were identified: Being in a void, Longing for old self by the participant: Longing for previous partner by spouse.

Being in a void refers to the period of ICU stay the participants couldn't remember. One participant was troubled by the fact that couldn't remember the time he was taken to the hospital to the time he was just about to be transferred to the high dependency unit. He had an ICU LOS of 20 days of which 14 were unaccounted for as he was unconscious. He described that part of his life as being in a void.

> *"Yea a void…//…no memory of intensive care at all…//… don't remember a thing at all…//… nothing at all. Fourteen days of no memory…//… don't remember intensive care…//… just a void. I wish I could you know just a void…"*

William (Participant 1)

Longing for old self elucidates the participants' yearning to return to their pre-critical illness self. The self that was vibrant, independent and full of both sort and long-term memory. Participant was frustrated that he could only remember things that happened before he fell sick. He also longed for the strength he had prior to his critical illness. The participant felt depressed and suicidal at times due to the loss of his identity as he knew himself before ICU hospitalisation.

> *"Don't remember as I used to…//…them things of the past are good yea…. Not after the hospital. Can't do anything just depressed…//…yea no motivation to do anything…//… just watch telly. I sometimes think why not end all. Not the way to live yea not the way"*

William (Participant 1)

Longing for the previous partner highlights the desire of the participants' spouse to be the way she knew him before he became sick. She narrated how frustrated she was that her husband was a different man after ICU.

> *"He just…//…I mean he used to go to work cause he was a shift worker. He was working 12-hour shifts. He used to cook dinner for everybody at work, didn't ya'? And he had two yards that he used to do besides ours. You know? That was his pocket money sort of thing, and he loves the garden and what have you, but he just…//… I can't get him interested in doing it anymore. . I mean I'm saying he won't go for a walk by himself…//… he doesn't do anything. I mean some things that he used to eat, he doesn't eat now. And I don't know why he doesn't eat them now. He -- he um, watches the telly all the time. And all -- and I notice I'll ask him to get him something. He doesn't know what I want. Every now and then, he gets cranky, you know? He don't want to be here, you know?"*

Meredith (Participant 2)

She wasn't sure if the medication contributed to his changed way of living *"could it be the medicine he was given in ICU. He was asleep for a long time you know".*

These findings could not be discussed in relation to other literature as they are not generalizable. The participant sample was too low.

Discussion

Sedation management remains the same compared to other ICUs [4,13]. Our study demonstrated that midazolam and propofol remain the primary sedation agents followed by dexmedetomidine. Analgesic agents also remain similar to other ICUs across the nation and the world. Morphine and fentanyl were used mostly. The GCS, RAAS and VSR were mostly used to assess sedation and the numerical scale was used to assess patients' level of pain. Results are similar to previous studies [4,13].

There was an association between sedation management, hepatic and renal dysfunction with patient ventilator, ICU and hospital LOS. The association between hepatic and renal dysfunction and patient long ventilator, ICU and hospital LOS is consistent with [10,14]. Interestingly, while finding could be related to primary diagnoses and comorbidities, the APACHE and SAPS scores were moderate to high. Additionally, these participants also scored highly on the HADS. As there was not much literature examining relationships of sedation and hepatic and renal function data, this study's comparison with other studies is limited on this finding.

The fact that this study showed that drugs used in sedation management were consistent with those used in other ICUs both nationally and internationally studies [1,2,8] means that sedation management remains the same across the world and as such, global standards could possibly be related with global ICU issues such as the association between sedation management with short and long-term outcomes of ICU patients. At a global level, our study underscores the prevalence of anxiety and depression in post ICU patients [15-17]. However, the findings of this study call for a bigger study for them to be generalizable [18-26].

Conclusion

The findings from both quantitative and qualitative research methods demonstrate that there is a relationship between sedation dosing, patient hepatic and renal function status and short and long-term outcomes of ICU patients. Although only one (n=1) patient stated he suffered from depression and had thoughts of suicide, and others scoring high on the HADS scale, there remains a summation that sedation management, hepatic and renal dysfunction are associated with long ventilator, ICU and hospital LOS, and elevated HADS scores. Despite the numbers being low, this study's results resonate with larger studies. A more robust multicentre study examining sedation management and hepatic and renal function data in relation to ventilator, ICU and hospital LOS, and HADS scores is needed. This study's strength despite being small, lies in its examination of sedation management, patient's hepatic and renal function data in relation to ventilator, ICU and hospital LOS, and elevated HADS scores including conducting an in-depth face to face interviews.

Being is a single centre pilot study with a small sample limits this study from being representative of a larger population. However, its findings resonate with larger studies and brings anecdotal evidence that high sedation dosing with elevated hepatic and renal function data is associated with long ventilator, ICU and hospital LOS, and elevated HADS scores.

Recommendations for Clinical Practice

Careful monitoring of hepatic and renal function results to ensure optimal safety and efficiency of sedative and analgesic drugs in critically ill patients, particularly in the presence of hepatic and/or renal dysfunction is encouraged.

The use of Sedation tools is recommended to ensure safe sedation management.

Judicious sedation and analgesic assessment and titration is recommended.

Collaboration between nurses and doctors in management of sedation and monitoring of hepatic and renal function for better patient short and long-term outcomes is encouraged.

Highlight

Hepatic and renal function status and sedation management impact patient short and long-term outcomes.

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