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Title:

What is the relationship between elements of ICU treatment and memories after discharge in adult ICU survivors?

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Abstract

Objectives: Patients admitted to an intensive care unit (ICU) often experience distressing memories during recovery that have been associated with poor psychological and cognitive outcomes. The aim

of this literature review was to synthesise the literature reporting on relationships between elements of ICU treatment and memories after discharge in adult ICU survivors.

Review method used: Integrative review methods were used to systematically search, select, extract, appraise and summarise current knowledge from the available research and identify gaps in the literature.

Data sources: The following electronic databases were systematically searched: PubMed, Ovid EMBASE, EBSCOhost CINAHL, PsycINFO and Cochrane Central Register of Controlled Trials. Additional studies were identified through searches of bibliographies. Original quantitative research articles written in English that were published in peer-review journals were included.

Review methods: Data extracted from studies included authors, study aims, population, sample size and characteristics, methods, ICU treatments, ICU memory definitions, data collection strategies and findings. Study quality assessment was based on elements of the Critical Appraisal Skills Programme using the checklists developed for randomised controlled trials and cohort studies.

Results: Fourteen articles containing data from 13 studies met the inclusion criteria and were included in the final analysis. The relatively limited evidence about the association between elements of ICU treatment and memories after ICU discharge suggest that deep sedation, corticoids and administration of glucose 50% due to hypoglycaemia contribute to the development of delusional memories and amnesia of ICU stay.

Conclusions: The body of literature on the relationship between elements of ICU treatment and memories after ICU discharge is small and at its early stages. Larger studies using rigorous study design are needed in order to evaluate the effects of different elements of ICU treatment on the development of memories of the ICU during recovery.

Key words: Memory, delusion, psychological recovery, critical care, evidence based nursing

Introduction

Patients admitted to an intensive care unit (ICU) often experience distressing memories during recovery. Specifically, delusional, factual and emotional memories are frequently reported.¹⁻³ Delusional memories correspond to the recall of unreal events such as hallucinations, nightmares and paranoia, which have been estimated to be present in about 20% - 48% of patients.^{3,4} Factual memories are the recall of real events that occurred during patient's intensive care treatment such as the presence of an endotracheal tube and mechanical ventilation; proportions of patients who recall factual memories vary significantly from 18% to 96%.^{1,2} Emotional memories involve the recall of feelings such as anxiety, fear, suffocation and pain and have been reported by highly variable proportions of patients, ranging from 9% to 88%.^{1,2,5,6} Lack of memory of ICU events has also been reported in about 18-38% of patients.^{1,7}

Memories of ICU treatment play a significant role in the development of post-intensive care syndrome (PICS), in other words the development of a syndrome that is characterised by “new or worsening problems in physical, cognitive or mental health status arising after a critical illness and persisting beyond acute care hospitalisation.”⁸ Memories are thought to specifically affect the psychological and cognitive components of recovery of ICU survivors.^{9,10} For instance, delusional and emotional memories have been associated with the development of symptoms of anxiety, depression and posttraumatic stress after ICU discharge.¹¹⁻¹⁷ The role of factual memories is unclear, with them being identified as protecting patients from anxiety and posttraumatic stress symptoms in some cohorts,¹¹ while in others factual memories have been associated with poorer psychological health during recovery.¹⁸ The number of distressing memories that patients recall was identified as a significant factor for posttraumatic stress symptoms.^{6,16,19,20} The association between cognitive functioning and memories of the ICU has also been explored. An improved cognitive functioning after ICU discharge was found to be significantly associated with having no recollections of the intensive care experience.²¹

A range of elements of ICU treatment have been proposed as affecting psychological health, including the number and type of memories of ICU. These elements of care have included specific categories of medications such as anti-inflammatory medications, for example hydrocortisone²²⁻²⁴ and sedation and analgesic agents, for example midazolam and opioids.^{1, 2, 25} Further, a link between the level of sedation and psychological health has been proposed, although the evidence of that relationship remains unclear.²⁶ Given the potential influence of aspects of ICU treatment on memories, and the link between memories of ICU and PICS, it is appropriate to explore these links with a view to adapting our practice to improve memories. A review addressing this topic could not be located in the current literature. The aim of this literature review was to synthesise the literature examining relationships between elements of ICU treatment and memories after discharge in adult ICU survivors.

Method

Integrative review methods were used to systematically search, select, extract, appraise and synthesise the available research.²⁷

Eligibility criteria

Primary research articles were included in the review if they measured the relationship between specific ICU treatments and memories reported by adult ICU survivors. Studies were excluded if they were not written in English. ICU treatments were defined as interventions administered to patients during admission to a critical care unit e.g. mechanical ventilation, use of invasive devices and administration of medications. ICU memories were defined as per the study authors, and included factual and delusional memories of the survivors' time in a critical care unit.¹¹

Search methods

PubMed, Ovid EMBASE, EBSCOhost CINAHL, PsycINFO and Cochrane Central Register of Controlled Trials were systematically and independently searched in May 2015. Medical Subject Headings (MeSH) were amnesia, memory, intensive care units, critical care, critically ill, critical

illness, and intensive care. Additional studies were identified through searches of bibliographies. Searches were performed without year restrictions but were limited to human studies. Titles and abstracts were scanned for relevance and eligibility using the *a priori* eligibility criteria. The search was undertaken by one author (AU) using search terms developed by the review team. Selection of articles based on the inclusion and exclusion criteria was completed by two authors (AU and LMA) independently, with results compared and disagreements discussed and resolved by the whole team.

Data extraction and quality appraisal

A data extraction form was developed by the study authors (AU and LMA) and applied to each of the included studies. For each paper the author, study objective, population, sample size and characteristics, methods, ICU treatments, ICU memory definitions, data collection strategies, findings and study quality were extracted by study authors (MIC, AU, KC). Study quality assessment, including the elements of validity, significance and usefulness, was based upon elements of the Critical Appraisal Skills Programme (CASP) checklists relevant to each included study.²⁸

Data synthesis

Data from the included studies were categorised and summarised to product a coherent and logical summary across the different categories of ICU treatment.

Results

Following database and bibliographic searching 2748 titles were identified. This number was reduced to 1548 titles after duplicates were removed (Figure 1).²⁹ The abstracts of these titles were reviewed and 64 full text articles examined. A further 50 articles were excluded due to not focusing on the review question, with 14 articles (13 studies; one duplicate publication with some additional results²⁻¹⁸) included in the synthesis of results. No meta-analyses were able to be undertaken due to the diversity of designs, interventions examined and instruments used to measure memories; this resulted in the absence of multiple studies examining sufficiently similar questions to enable data to be combined.

<Insert Figure 1>

Randomised controlled trials and cohort studies were the most commonly used designs in the 13 included studies (Table 1). Sample sizes were highly variable, ranging from 11 to 313 participants. Instruments used were also highly variable and follow-up was conducted between 3 days and 5 years after ICU discharge. Studies generally had variable levels of both bias and usefulness, with this latter aspect often limited by small sample sizes (Table 2).

Sedation, both in regard to the agents used and the depth of sedation, was the primary intensive care intervention examined in relation to memories after ICU and was the focus of eight studies.^{1-3, 17, 18, 30-33} Consequently, the most common theme that was identified focused on sedation and analgesia. The effect of other medications and the duration of mechanical ventilation were also explored in a small number of studies.

<Insert Table 1>

<Insert Table 2>

Sedation and analgesia

Sedation and analgesia have been explored as possible factors associated with patients' ability to recall ICU events with most of the evidence indicating that these therapies have some influence in this area.^{2-4, 17, 32, 34} Depth of sedation, as measured using various sedation assessment scales, has been proposed as having a significant impact on patients' recall of ICU events. Deeply sedated patients reported amnesia of their ICU stay (OR 1.60, 95% CI 1.35-1.91, $p < 0.0001$),² had "trouble remembering important parts of the stressful experience" (37% vs 13%, $p = 0.01$),³² and reported more repeated, disturbing memories (18% vs 4%, $p < 0.05$).³² Further, more deeply sedation patients reported delusional memories (33% vs 6%, $p = 0.09$)³ (OR 1.76, 95% CI 1.14 – 2.72, $p = 0.008$)² 3-5 days after ICU discharge.

In contrast, the depth of sedation appeared to influence patients' perception of stressful experiences during ICU treatment with the more awake patients reporting more stressful or bothersome memories,

as described on the ICU-stressful experiences questionnaire.¹⁸ These findings are not consistent with Weinert and Sprenkle⁷ identifying no association between intensity of sedation administration and ICU recall in a cohort of medical-surgical ICU patients, although they did report a weak association between increased wakefulness and factual ICU recall ($r^2=0.03 - 0.11$, $p<0.05$).⁷

The association between specific medications such as benzodiazepines, opioids and propofol during ICU treatment and memories of ICU has also been investigated although again, the evidence is conflicting. A retrospective study including 161 cardiac surgery survivors reported a significant association between delusional memories and midazolam infusion (OR 3.51 95%CI 1.59-7.75, $p=0.002$) 2-5 years post ICU discharge.⁴ On the contrary, an explorative multicentre investigation including 239 trauma participants found no such relationship between delusional memories and benzodiazepines, opioids, and propofol in multivariable analysis.³⁴ Similarly, no statistically significant difference was reported in memories by 17 patients enrolled in a pilot RCT designed to examine the effect of midazolam versus isoflurane on memories, although there was a trend towards less memories of hallucinations or delusions in the group treated with isoflurane.¹⁷ Further, in 152 medical-surgical ICU patients the influence different regimens of sedation and analgesia (Group A: no morphine and <2 doses of a benzodiazepine; Group B: morphine without other sedative drugs, and Group C: morphine and other sedative drugs) was examined.¹ It was concluded that analgesia (morphine) and sedation (propofol, benzodiazepines and promazine) did not influence the incidence of factual, sensation, and emotional memories of this cohort.¹

The discrepancies in these different results might be explained by the differences in the design of these studies (prospective versus retrospective cohorts versus pilot RCT) and the characteristics of the samples investigated (trauma, cardiac surgery and general ICU patients). For example, delusional memories were reported by 26% of the trauma patients³⁴ compared to 48% of the cardiac surgery group.⁴ In addition, benzodiazepines (no specific information provided about what medications were used) were administered to 24% of the trauma patients³⁴ compared to 32% of the cardiac surgery group who received midazolam.⁴ Delusional memories were not specifically reported in the medical-

surgical ICU group¹ but emotional memories incorporating hallucinations, nightmares, dreams and feeling confused or down were reported in 15% of the group receiving <2 doses of benzodiazepines and 32% of the group receiving unlimited sedatives. In the cardiac surgery cohort both the prevalence of delusional memories (48%) and administration of midazolam (32%) were much higher than the trauma cohort.⁴ Of note, the trauma patients had an average ICU LOS of approximately 4 days³⁴ while the cardiac surgery patients remained in ICU for an average of 5 (non-dreamers) or 7 days (dreamers).⁴

Different sedation strategies such as sedation protocols or sedation interruption have been proposed as influencing patients' recall of their time in ICU. Despite the theoretical basis for such links, no difference in the recall of ICU experiences including recollections of fear, anxiety and pain measured on a locally developed instrument were reported by 21 patients enrolled in a pilot RCT.³⁰ This pilot study was designed to examine the effect of protocolised sedation versus protocolised sedation and daily sedative interruption on memories, with findings indicating that recall was not correlated with sedation scores or doses of sedation received.³⁰ Similarly, Kress and colleagues³¹ found no difference in the number of usual care patients versus sedation interruption patients who recalled being in (68% vs 69%, $p=1.0$), or waking in (26% vs 0%, $p=0.06$), ICU. Both of these studies were small ($n= 21$ and 32), with limited ability to detect meaningful differences.

The relatively limited evidence regarding sedation and analgesia in ICU patients suggests that these therapies contribute to the patients' ability to recall ICU events and to the development of delusional memories and amnesia of ICU stay. However, the evidence is conflicting and inconclusive. Larger studies exploring different aspects of sedation and their association with the development of memories of the ICU during recovery are needed.

Other medications

The theory that the exogenous administration of stress doses of corticosteroids provides a protective effect against the development of traumatic memories was tested in two small RCTs of cardiac

surgical ICU patients.^{24,35} Although some other benefits such as shorter ICU LOS and improved quality of life scores were seen in those receiving corticosteroids, no significant difference was found in the incidence of traumatic memories in either of these RCTs. In contrast, a significant association between corticoids and delusional memories (OR 10.2 95%CI 1.11-93.0, p=0.04) was identified in a small (n=161) retrospective cohort study.⁴ Although this finding was statistically significant, it is important to note the limitations of the study design and that only eight out of 161 patients received corticoids during ICU, with six of these patients reporting delusional memories.⁴ In this same study a significant association between delusional memories and the administration of intravenous 50% glucose to treat hypoglycaemia (OR 15.5, 95%CI 3.19-66.4) was identified. To aid understanding of these results it would have been beneficial if data regarding the severity of hypoglycaemia were presented since one could speculate that the real risk factor for delusional memories was hypoglycaemia instead of the administration of 50% glucose. Another point to consider is the surprisingly high proportion (35%) of participants who received boluses of glucose during ICU treatment, which could reflect selection bias with participants not being representative of the usual ICU population.

Duration of mechanical ventilation and ICU stay

The presence or duration of mechanical ventilation has also been proposed as influencing memories after ICU, particularly in regard to the development of traumatic or distressing memories or the absence of memories. The duration of mechanical ventilation is often related to the length of ICU stay which may be used as an indirect marker of this treatment. Approximately half of the 206 mechanically ventilated general ICU patients who had memories of the ICU recalled discomfort associated with the endotracheal tube that were bothersome and those who were bothered by stressful memories of the ICU had longer ICU LOS.¹⁸ In contrast, although ventilator support was linked to delusional memories on univariate analysis in 239 trauma patients, it did not retain statistical significance when incorporated into multivariable analysis.³⁴ Similarly, mechanical ventilation was not associated with factual, sensational or emotional memories in 152 ICU patients.¹

Measures and methods used to assess patients' memories

Memories were measured using a variety of instruments including structured interviews,^{1, 31, 36} the ICU stressful experience questionnaire (ICU-SEQ),^{2, 3, 18} ICU memory tool (ICU-MT)^{2, 3, 17, 18, 34}, Posttraumatic Stress Symptoms 10-Question Inventory PTSS-10^{23, 35} and author-developed surveys (Patients Recall Questionnaire³⁰ and ICU amnesia tool⁷ or questions.³¹ A modified version of the ICU-MT (with no validation of modification) was used in one study.⁴ In another study no specific instrument to assess patients' memories was used, but two items of the Post-Traumatic Stress Disorder Checklist (instrument to assess symptoms of posttraumatic stress) that address memories.³² Memories were assessed at varied time points in the included studies, from 72 hours³⁰ to 5 years⁴, with the most common follow-up being approximately six months after discharge (Table 1).

Discussion

The relationship between intensive care interventions and memories of ICU after discharge was examined in this review. Sedation practice was the most common intensive care treatment investigated in relation to the development of memories of ICU, but the evidence was inconsistent for the elements of care (e.g. deep versus light sedation, different sedative medications, daily sedation interruption). Deep sedation during ICU treatment frequently was associated with amnesia and delusional memories while light sedation was associated with a greater risk of perceiving stressful experiences more bothersome.^{2, 3, 18, 32} Despite these identified associations, no such association was reported in one study.⁷ This relationship between level of sedation and memories after ICU is particularly important to understand given the move towards lighter sedation over the past decade.²⁶

When considering the specific sedative agents, benzodiazepines, including midazolam, were associated with the development of delusional or hallucination-like memories of ICU in some settings.^{4, 17} This relationship with delusional memories warrants further exploration since the available evidence is small and inconsistent. Although this relationship was found in two included studies, it was not identified in others.^{1, 34} Since these four studies differ in essential aspects of their

design (e.g. prospective vs. retrospective; cardiac vs. trauma vs. general ICU patients), the comparison between them might not be appropriate and therefore the interpretation of the evidence in regard to benzodiazepines is inconclusive.

Different sedation strategies such as using sedation protocols, daily sedation interruption and various sedative agents such as midazolam, isoflurane, morphine and propofol were tested to elucidate their association with memories of ICU.^{1, 17, 30, 31} No particular strategy was found to be better or worse than others. Nevertheless, these studies had relatively small sample sizes with restricted ability to determine significant differences. Future studies testing different sedation strategies should incorporate larger sample sizes in their design so as to be able to detect significant effects.

Interventions other than sedation that have been examined in relation to ICU memories were corticosteroids and intravenous 50% glucose to treat hypoglycaemia. The evidence on the association between stress doses of corticosteroids and memories of ICU is limited. As slightly different aspects of memories of ICU were explored in these studies, the comparison between them is difficult. In two RCTs the factor explored was the incidence of traumatic memories (memories of pain, nightmares, anxiety and difficulty breathing) compared with the presence of delusional memories in one retrospective study.^{4, 24, 35} Delusional memories were associated with the administration of corticosteroids, but no association between hydrocortisone and the incidence of traumatic memories of anxiety, pain, nightmares and difficulty breathing was found in the RCTs.

Intravenous 50% glucose to treat hypoglycaemia was associated with delusional memories.⁴

Unfortunately, information regarding the severity of hypoglycaemia was not presented and it could be speculated that 50% glucose might be a confounder and that hypoglycaemia might have been the real risk factor for delusional memories. In addition, the high proportion of participants treated with this medication suggests selection bias.

No relationship between mechanical ventilation and delusional, factual, sensational or emotional memories was found in the literature.^{1, 34} Despite the evidence being limited to two studies, the lack of relationship is consistent.

This review is limited by the nature of the question that guided the process; only those studies that measured an association between ICU interventions and memories were considered, resulting in the review being limited to studies designed to measure variables quantitatively. Also to note, a range of interventions that have the potential to influence memory have not been investigated, for example early mobilisation and use of alternative sedative agents such as dexmedetomidine. Further, scales that assess either memory or perceptions of the intensive care experience generally have not undergone rigorous psychometric testing thus limiting reliability and validity of findings. A number of scales exist and this also makes it difficult to extrapolate consistent findings with some assessing memories of specific events or treatments and others perceptions of the experience. What however does seem clear is that patients can be distressed by their memories whether these are factual or delusional,^{11, 37, 38} and that these memories have been consistently linked to poorer outcomes.^{13, 18, 39} The strength of that association has still to be established. Patients who have greater awareness may report troublesome discomforts of thirst, having tubes and being unable to communicate^{1, 37} whereas patients who experience delusions often find these persecutory and there are frequent reports of staff trying to 'kill' patients or do harm to them. Whether these differences in perceptions or memories are related to depth of sedation is not clear, although the evidence that deep sedation leads to limited recall of ICU and increased incidence of delusional memories is reasonably consistent.^{2, 3, 18, 32} Participants in the included studies were enrolled during their hospital admission, with the exception of one retrospective study,⁴ however the timing of follow up varied from prior to ICU discharge to 5 years later, with the most common follow-up being approximately six months after discharge. Given the highly variable methods of assessing memory it is not possible to assess the effect of these differences, however it is highly likely that it influences the content and clarity of recall.

Implications for practice and research

Although there is currently limited and inconsistent evidence, the influence of sedation on memories has moderate support. Deep sedation is linked to limited recall of ICU and increased incidence of delusional memories. This suggests that strategies to minimise sedation should continue to be developed and implemented. Despite this broad principle, there is currently conflicting evidence regarding the role of different sedation strategies such as daily sedation interruption or the benefit or disadvantage of specific sedative agents and additional research involving larger sample sizes and effective control of related interventions is urgently needed.

Further, scales that assess either memory or perceptions of the intensive care experience generally assume that patients who recall being ‘attacked’ or have ‘people trying to hurt me’ are delusional however this might not be the case. Instead patients may be interpreting behaviours in different, and individual, ways. This variation in experience should be considered as we research and implement evolving strategies such as patients being more alert and oriented during ICU admissions – this experience may affect each patient differently.

Conclusion

Identification of elements of ICU treatment that affect memories during recovery has the potential to influence how care is delivered. Aspects of care that have been examined include sedation and analgesia, other medications and mechanical ventilation. Although the evidence was inconsistent, and the numbers of participants was frequently small, it appears that some aspects of treatment may influence the absence of memory or development of delusions and hallucinations.

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Table 1 – Relationships between ICU treatment and memories of ICU survivors

Author details	Aim	Participants & Design	Outcome measure	Results	Comments including strengths & limitations
Henderson et al. 1994; Australia ³³	To assess the effects of adding low dose midazolam to papaveretum on memory recall and duration of ventilation in drug paralysed post-operative patients	100 post-operative patients; blinded RCT; recall assessed just prior to ICU discharge	Locally developed 'experience' questionnaire (no validation)	No difference in recall in regard to pain, noise, anxiety, discomfort, memory. Duration of ventilation no different (25 vs 26 hrs, $p>0.05$).	No control of other aspects of care; asked patients to recall 'period of drug paralysis' so their recall might relate to any period of ICU care; conducted in a time where routine paralysis was common and therefore not relevant to the current practice environment.
Capuzzo et al. 2001; Italy ¹	To investigate the relationship between analgesia, sedation and memory of intensive care	152 ICU patients with LOS > 24 hours; prospective cohort study with follow-up 6 months after hospital discharge in 1 hospital	Structured interview to assess memories (factual, sensation and emotional) based on the ICU-MT. Quality of life (locally developed instrument)	No significant difference in the incidence of factual, sensation and emotional memories between the 3 sedation groups (Group A: no morphine/0-2 doses benzodiazepines; Group B: morphine without other sedatives; Group C: morphine and other sedatives). Although bivariate analysis indicated patients reporting at least 1 emotional memory were more likely to be female, emergency admission, have infection/sepsis and receive corticosteroids, only gender was significant in logistic regression.	48 eligible patients not interviewed due to loss-to-follow-up (36), terminally ill (4) and cognitive impairment (8) – non-participants were more likely to be post-surgery with a longer ICU and hospital LOS; convenience sampling used for recruitment in single centre.
Kress et al. 2003, USA ³¹	To search for evidence that daily interruption of sedation was associated with long-term psychological harm.	32 mechanically ventilated medical ICU patients; participants recruited from previous RCT as well as contemporaneous cohort were followed up 6 months after discharge	Structured interview by clinical psychologist plus self-report measures (IES-R, SF-36, STAI, BDI, PAIS) Locally developed questions to assess recollection of ICU	Many patients recalled being in ICU when questioned in their hospital stay (68% control versus 69% intervention, $p=1.0$); there was a trend towards more patients in the control group recalling waking in ICU when questioned at 6 months (26% control versus 0% intervention, $p=0.06$).	Specific methodology or instruments were not used to measure memories of ICU – the information appears to have been collected during the follow-up interview; potentially biased cohort given small proportion of eligible patients enrolled.
Pierce et al. 2004; United	To examine the association of	161 cardiac surgical patients with ICU	Modified ICU-MT with no validation	Patients were categories as 'dreamers' (1 or more memories of dreams, nightmares,	Clinical factors collected through retrospective chart review; 161 of

Kingdom ⁴	delusional and real memories with pre-operative and post-operative factors.	LOS >4 days; retrospective cohort study with follow-up 2 – 5 years after surgery in 1 hospital	of modification	thoughts that others were trying to inflict harm, were plotting against patient or that patient had travelled after surgery) or ‘non-dreamers. Factors positively associated with ‘dreamers’ included treatment with intravenous 50% glucose, midazolam, steroid therapy and episodes of sepsis, with the development of new neurological signs exerting a protective effect.	423 possible patients recruited (89 died, 59 whose GP refused assent, 90 no response); variable follow-up time frame.
Schelling et al. 2004; Germany ²³	To examine whether stress doses of hydrocortisone after cardiac surgery reduce long term incidence of chronic stress, PTSD and traumatic memories	91 cardiac surgery patients; RCT with follow-up at 2-3 days, 1 week and 6 months (n=48) after ICU in 1 hospital	PTSS-10	No significant difference in number and categories of traumatic memories between patients in hydrocortisone and control groups: nightmares (23% vs 36%, p=0.36), pain (19% vs 9%, p=0.43), respiratory distress (19% vs 27%, p=0.73), anxiety/panic (31% vs 40%, p=.33).	Participants and clinical staff blinded to group allocation; validated traumatic memories questionnaire;
Ringdal et al. 2006; Sweden ³⁴	To describe trauma patients’ memories of ICU and identify factors associated with delusional memories	239 trauma ICU patients; prospective cohort study with follow-up 6 – 18 months after ICU discharge in 5 hospitals	ICU-MT	Patients with clear recollection of ICU had shorter ICU LOS, were less likely to require mechanical ventilation and have shorter duration of mechanical ventilation, and were less likely to receive sedatives. Patients with delusional memories were younger, had longer ICU LOS, higher temperature; lower haemoglobin and more likely to have had renal failure, surgery, ventilator support, sedatives and analgesics.	239 of 344 eligible participants recruited (66 did not reply, 39 declined; non-responders had shorter ICU LOS but otherwise did not differ from the final participants); analysis was limited to bivariate analysis with no multivariable analysis reported.
Weis et al. 2006; Germany ³⁵	To determine whether hydrocortisone administration reduced chronic stress symptoms after cardiac surgery	36 high risk cardiac surgery patients; RCT with 6 month follow-up after ICU in 1 hospital	PTSS-10 SF-36	Patients who received hydrocortisone had a shorter ICU LOS, lower TISS scores, required less norepinephrine and a trend towards lower pro-inflammatory cytokine IL-6 as well as higher quality of life scores and lower chronic stress symptom scores. Number and type of traumatic memories did not differ between the two groups (p≤.33).	Participants and clinical staff were blinded to group allocation; 28 / 36 patients followed up (2 incomplete data, 6 did not return questionnaire) with no differences between those who completed the study or not; previously validated memory instrument used.
Samuelson et al. 2006 &	To investigate the relationship between	313 intubated mechanically	ICU-MT ICU-SEQ	Patients with no recall of ICU (18%) were older and had fewer periods of wakefulness	250 of 313 patients completed the study; convenience sampling used to

Samuelson et al. 2007; Sweden ^{2,18}	(i) memory and intensive care sedation (ii) recall of stressful experiences and intensive care sedation	ventilated adults admitted to ICU for >24 hours; prospective cohort study with follow-up 6-10 days after ICU in 2 hospitals		(MAAS 0 – 2) than those with memories of ICU (82%). Patients with delusional memories (34%) had longer ICU stay, higher baseline severity of illness, higher proportions of MAAS 4 – 6 and more midazolam than those with recall of ICU but no delusional memories. Patients with more periods of wakefulness (MAAS 3), longer ICU stay and emergency admissions recalled stressful experiences as more bothersome.	recruit participants; patients who were lost to follow-up were more frequently emergency admissions and older than those retained in the study; previously validated ICU Memory Tool used to measure recall; follow-up only 6 – 10 days after ICU.
Samuelson et al. 2008; Sweden ³	To assess the presence of stressful memories in light versus heavy sedation	36 mechanically ventilated post-operative patients; RCT with 2 month follow-up after ICU in 1 hospital	ICU-MT ICU-SEQ IES-R	No significant difference in memory between light (MAAS 3 – 4) and heavy (MAAS 1 – 2) sedation patients; trend towards more delusional memories in the heavy sedation group (33% vs 6%, p = 0.09); analysis excluding prolonged ICU stay showed higher prevalence of delusional memories in heavy sedation group (31% vs 0%, p = 0.04).	Previously validated ICU Memory Tool used to measure recall; follow-up only 5 days after ICU; pilot study with small participant numbers.
Weinert et al. 2008; USA ⁷	To determine the relationship between critical illness factors and ICU recall and symptoms of post-traumatic stress disorder	277 adult ICU patients; prospective cohort study with follow-up 2 and 6 months post ICU discharge	ICU amnesia score (developed by study authors – limited validation of this tool); Posttraumatic stress diagnostic scale	Intensity of sedation administration was not associated with ICU recall although there was weak association between increased wakefulness during mechanical ventilation and factual ICU recall (r ² =0.03-0.11, p<0.05).	Only 90 of 277 patients provided data for 2 and 6 month follow-up; those who completed 2 month follow-up were more likely to be treated in the surgical ICU, had shorter duration of mechanical ventilation and better mental status prior to intubation; recall of ICU experience measured using appears to have been locally developed with no validation described.
Sackey et al. 2008; Sweden ¹⁷	To compare memories of ICU after sedation with intravenous midazolam or inhaled isoflurane	40 mechanically ventilated general ICU patients; RCT with follow-up 6 months after ICU in 1 hospital	ICU-MT HADS IES WB	Trend towards less memories of hallucinations or delusions in the isoflurane group although this did not reach statistical significance (2/10 vs 5/7, p = 0.06). No significant differences between the groups in regard to memories of feelings or factual events.	Only 17 of 40 patients provided data (11 died; 12 non-responders); no control of other related factors such as opioid medications and ICU LOS.

Treggiari et al. 2009; Switzerland ³²	To determine if light sedation, compared to deep sedation, affects subsequent patient mental health	137 patients requiring mechanical ventilation (129 included in analysis); RCT with follow-up at hospital discharge and 4 weeks	PCL IES-R HADS	At hospital discharge more patients in the deep sedation group had “trouble remembering important parts of the stressful experience” (37% vs 13%, p = 0.01), this remained similar (37% vs 14%, p=0.02) at 4 weeks; similar patterns were reported in regard to “repeated, disturbing memories of the stressful experience” (18% vs 4%; p = 0.05 at both discharge and 4 weeks)	No specific instruments used to assess patients’ memories however 2 items in the PCL address memories;
Ethier et al. 2011; Canada ³⁰	To evaluate recall of ICU stay in patients managed with 2 sedation strategies: a sedation protocol or a combination of sedation protocol and daily sedation interruption	21 adult ICU patients managed with sedation protocol or no sedation protocol; pilot RCT with follow-up 72 hours after ICU discharge	Patients Recall Questionnaire (develop by study authors – no validation of this tool)	No significant differences in the recall of ICU experiences between the 2 groups. More than 50% of patients in both groups recalled experiencing pain, anxiety or fear while in the ICU and 48%, 33% and 29% of the 21 patients had no memories of endotracheal tube suctioning, being on a breathing machine or being bathed, respectively.	Convenience sampling, with 26 of a potential 39 patients approached and 21 patients enrolled; Non-validated, locally developed, instrument used to measure short-term recollection of ICU; Extremely short-term (72 hours) follow-up.

MAAS – Motor Activity Assessment Scale; ICU-MT: ICU Memory Tool; IES-R: Revised Impact of Event Scale; SF-36: Medical Outcomes Study SF 36 item short-form health survey; STAI: State and Trait Anxiety Inventory; BDI: Beck Depression Inventory; PAIS: Psychological Adjustment to Illness Score; HADS: Hospital Anxiety and Depression scale; IES: Impact of Event Scale; WB: Well-Being Index; ICU-SEQ: ICU Stressful Experiences Questionnaire; PTSS-10: Posttraumatic Stress Symptoms 10-Question Inventory; PCL: PTSD Checklist

Table 2: Study quality appraisal using CASP criteria

Author details	Method	Validity	Significance	Usefulness
Henderson et al. 1994 ³³	RCT	Selection bias: Unclear Measurement bias: High Assessment of confounding variables: Low Longevity of follow-up: Low	Reporting bias: Unclear Imprecise results	Low Usefulness
Capuzzo et al. 2001 ¹	Prospective cohort	Selection bias: Low Measurement bias: Unclear Assessment of confounding variables: High Longevity of follow-up: Unclear	Reporting bias: Low Precise results	Low usefulness
Kress et al. 2003 ³¹	Prospective and retrospective cohort	Selection bias: Low Measurement bias: High Assessment of confounding variables: Low Longevity of follow-up: Low	Reporting bias: Low Imprecise results	Low usefulness
Pierce et al. 2004 ⁴	Retrospective cohort	Selection bias: High Measurement bias: High Assessment of confounding variables: Unclear Longevity of follow-up: High	Reporting bias: Low Imprecise results	Low usefulness

Schelling et al. 2004 ²³	RCT	Selection bias: Low Performance bias: Low Attrition bias: Low Detection bias: Low	Reporting bias: Low Imprecise results	Moderate usefulness
Ringdal et al. 2006 ³⁴	Prospective cohort	Selection bias: Low Measurement bias: Low Assessment of confounding variables: Low Longevity of follow-up: Low	Reporting bias: Low Precise results	High usefulness
Weis et al. 2006 ³⁵	RCT	Selection bias: Low Performance bias: Unclear Attrition bias: Low Detection bias: Low	Reporting bias: Low Imprecise results	Moderate usefulness
Samuelson et al. 2006 & Samuelson et al. 2007 ^{2,18}	Prospective cohort	Selection bias: Unclear Measurement bias: Low Assessment of confounding variables: Low Longevity of follow-up: High	Reporting bias: Low Precise results	Moderate usefulness
Samuelson et al. 2008 ³	RCT	Selection bias: Low Performance bias: Unclear Attrition bias: low	Reporting bias: Low Imprecise results	Moderate usefulness

		Detection bias: Low		
Weinert et al. 2008 ⁷	Prospective cohort	Selection bias: Unclear Measurement bias: Unclear Assessment of confounding variables: Low Longevity of follow-up: Low	Reporting bias: Low Precise results	Low usefulness
Sackey et al. 2008 ¹⁷	RCT	Selection bias: Unclear Performance bias: High Attrition bias: Low Detection bias: Low	Reporting bias: Low Imprecise results	Moderate usefulness
Treggiari et al. 2009 ³²	RCT	Selection bias: Low Performance bias: Low Attrition bias: Low Detection bias: Unclear	Reporting bias: Low Imprecise results	Moderate usefulness
Ethier et al. 2011 ³⁰	RCT	Selection bias: Low Performance bias: Unclear Attrition bias: Low Detection bias: Low	Reporting bias: Low Imprecise results	Moderate usefulness

Figure 1: PRISMA Flow Diagram

