Original Article

A retrospective study of ketamine administration and the development of acute or post-traumatic stress disorder in 274 war-wounded soldiers*

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Summary

The objective of this study was to explore whether ketamine prevents or exacerbates acute or post-traumatic stress disorders in military trauma patients. We conducted a retrospective study of a database from the French Military Health Service, including all soldiers surviving a war injury in Afghanistan (2010–2012). The diagnosis of post-traumatic stress disorder was made by a psychiatrist and patients were analysed according to the presence or absence of this condition. Analysis included the following covariables: age; sex; acute stress disorder; blast injury; associated fatality; brain injury; traumatic amputation; Glasgow coma scale; injury severity score; administered drugs; number of surgical procedures; physical, neurosensory or aesthetic sequelae; and the development chronic pain. Covariables related to post-traumatic and acute stress disorders with a $p \leq 0.10$ were included in a multivariable logistic regression model. The data from 450 soldiers were identified; 399 survived, of which 274 were analysed. Among these, 98 (36%) suffered from post-traumatic stress disorder and 89 (32%) had received ketamine. Fifty-four patients (55%) in the post-traumatic stress disorder group received ketamine vs. 35 (20%) in the no PTSD group ($p < 0.001$). The 89 injured soldiers who received ketamine had a median (IQR [range]) injury severity score of 5 (3–13 [1–26]) vs. 3 (2–4 [1–6] in the 185 patients who did not ($p < 0.001$). At multivariable analysis, only acute stress disorder and total number of surgical procedures were independently associated with the development of post-traumatic stress disorder. In this retrospective study, ketamine administration was not a risk factor for the development of post-traumatic stress disorder in the military trauma setting.

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Introduction

Ketamine has unquestionable advantages for pre-hospital anaesthesia [1, 2]. It is not clear, however, whether ketamine administration could increase or decrease psychological stress associated with traumatic events and thereby affect the subsequent development

of acute stress disorder (ASD) and post-traumatic stress disorder (PTSD) [3]. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) has diagnostic criteria for both conditions [4].

Acute stress disorder is marked by disturbed sleep with nightmares and flashbacks, hyperarousal, emotional and autonomic hyperactivity, with symptoms lasting more than 2 days and less than 1 month; the intensity of ASD is a risk factor for progression to PTSD. Post-traumatic stress disorder is usually diagnosed 3–6 months after the traumatic event with four symptom clusters: intrusive recollections; avoidance of situations related to the trauma; alterations in cognitions and mood; and hyperarousal [5]. Sleep disorders are constant, with anxiety and depressive manifestations. A meta-analysis reported that the prevalence of PTSD was 23% among American veterans [6].

The peri-operative use of ketamine has been shown to reduce the prevalence of PTSD in burned soldiers [7]. However, subsequent data analysis by the same research team involving a larger cohort of patients found that intra-operative ketamine use had no effect on the incidence of PTSD [8]. Nevertheless, a recent randomised, controlled trial demonstrated that ketamine is able to treat symptoms of chronic PTSD [9]. Thus, it is not clear whether ketamine may modulate PTSD in traumatised soldiers. This lack of medical evidence led us to explore the influence of ketamine administration on the incidence of ASD and PTSD in a cohort of combat-injured soldiers.

Our primary objective was to investigate the association between ketamine administration to the war wounded and occurrence of PTSD. The relationship between ketamine administration and incidence of ASD was a secondary objective.

Methods

This was an observational, retrospective cohort study covering a 3-year period of the French military intervention in Afghanistan. All soldiers surviving an injury by firearms, explosive or in a military transport accident, were included. All characteristics of soldiers wounded between 1 January 2010 and 31 December 2012 were recorded at the different steps of the medical support. Data were retrospectively extracted from the database (780 items) created by one of the authors (CH) from cross-checked information sources of the French Military Health Service (FMHS):

1 OPEX records (overseas operations): fiche médicale de l'avant (medical record filed during battlefield care); registre santé de l'avant (health registry on battlefield care); records of the medical treatment facility in Kabul; and fichier OPEX (FMHS activity during operations abroad).
2 MEDEVAC (databases from medical evacuations): tactical MEDEVAC (within the military field) data from the helicopter battalion and the Patient Evacuation Coordination Centre; strategical MEDEVAC (between the Kabul and France) database from Villacoublay Air Force base and from health operational-level headquarters.
3 Medical records from all hospitals with surgical reports, psychiatric evaluations and rehabilitation summaries.
4 CABAT (Cellule Aide Blessés Armée de Terre) records (department in charge of the follow-up and assistance of the war wounded).
5 CESPA database (Centre Epidémiologie et Santé Publique des Armées) from the FMHS epidemiologic centre gathering the so-called F5 cards dealing with psychiatric problems in relation to a traumatic event.
6 Database from the pension office, allowing retrieving information of patients who benefit from a pension for invalidity, including soldiers having left the active military service.
7 All data were anonymised and processed electronically in accordance to the MR001 reference methodology, as required by the French National Commission (Informatique et Libertés).

The diagnosis of PTSD was carefully conducted. The FMHS is particularly involved with the identification, prevention, treatment and reparation of the psychological trauma in wounded soldiers. Tracing soldiers' exposure to risky situations is considered essential. Circumstances are noted in the soldier's medical record and in a register of the combat unit (Registre des constatations). Cases are reported for epidemiological monitoring with F5 cards. Between three

and six months after return from a war mission, the soldier completes a PTSD checklist (PCL-S) for first screening [10]. A complete, personal clinical interview is then undertaken under the supervision of a military physician. A psychiatrist always makes the final diagnosis of PSTD.

Analysis of the scientific literature allowed the selection of relevant covariables among the 780 basic items:

1 ASD;
2 explosion (blast);
3 associated fatality (at least one killed among the wounded);
4 injury severity score (ISS);
5 head injury (from scalp lesion to brain trauma);
6 initial Glasgow coma scale (GCS);
7 traumatic amputation;
8 administered drugs:

8.1 ketamine in the pre-hospital setting (battlefield) or at the field hospital with, whenever possible, the delivered dose (mg);
8.2 morphine at battlefield: subcutaneous (s.c.) or intravenous (i.v.) and at field hospital;
8.3 midazolam at battlefield and field hospital;

9 number of surgical procedures undergone from field hospital to metropolitan hospital;
10 physical, neurosensory or aesthetic sequelae; and
11 chronic pain.

All the individuals in whom a psychiatrist had made a diagnosis of PTSD were included in the PTSD group, with all other patients analysed in the no PTSD group. For quantitative variables, groups were compared with Student t-test or Mann–Whitney test. Binary variables were compared by a Chi-square test. Groups analysed according to ISS were compared with a Kruskal–Wallis test. All tests were two-tailed with a $p < 0.05$ considered as significant. Because a multivariate analysis had been planned, the Bonferroni correction was not applied. All covariates for which comparison provided a $p \leq 0.10$ were then included in a multivariable logistic regression analysis in order to detect which among them would be independently linked to the development of PTSD. No cut-off value was used and covariates were introduced either as numerical values or as dichotomic covariates. Significance was estimated with the Wald test. Two explanatory models were tested, one incorporating all covariates and a stepwise model in which non-significant variables were removed step by step from the model (backward approach). Statistical analyses were performed with the StatEL software (ad Science, Paris, France).

Results

The database comprised of 450 patients. Fifty-one died and of the remaining 399 patients, 274 patients (only two women, 0.7%) were analysed. Age was known for 257 patients, mean (SD) 30 (7) years in the PTSD group and 29 (6) years in the no PTSD group. Overall, 89 (32%) patients received ketamine, 98 (36%) were diagnosed with PTSD and 49 with ASD (18%) (Table 1). The 89 injured soldiers who received ketamine had a median (IQR [range]) ISS of 5 (3–13 [1–26]) vs. 3 (2–4 [1–6]) in the 185 patients who did not ($p < 0.001$). There was a greater number of surgical procedures undertaken in those soldiers who were most severely injured (Fig. 1).

Table 1 Injury severity score (ISS) relationship with the incidence of post-traumatic stress disorder (PTSD), administration of ketamine and number of surgical procedures performed in 274 soldiers wounded during military combat. Values are number (proportion) or median (IQR [range]).

	Injury severity score		
	1–15 n = 249	16–25 n = 13	26–50 n = 12
Diagnosis of PTSD	80 (32%)	10 (77%)	8 (67%)
Ketamine administration	64 (26%)	13 (100%)	9 (75%)
Number of surgical procedures	0 (0–1 [0–2])	5 (3–11 [1–23])	9 (7–18 [3–30])

Injury severity score and the number of surgical procedures were positively correlated ($p < 0.001$).

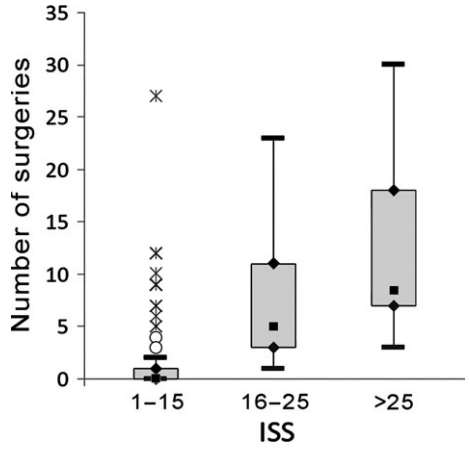

Figure 1 Box-and-whisker plot representation of the number of surgical procedures according to injury severity score (ISS). Median values are shown by ■, interquartile range by ◆, range by the whiskers; o represents atypical values and x extreme values.

Table 2 summarises the comparison between PTSD and no PTSD groups for the 16 covariates. Age, GCS, blast injury and associated fatality were not significantly related to PTSD. Soldiers in the PTSD group were more severely wounded, had a higher incidence of head injury and/or amputation, and were more likely to develop chronic pain, physical, neurosensory or aesthetic sequelae. The number of the surgical procedures they underwent was nearly six-times higher than in the no PTSD group. Soldiers in the PTSD group received twice as much morphine, three times as much ketamine and six times as much midazolam than patients in the no PTSD group.

Fifty-four patients (55%) in the PTSD group received ketamine, which was 2.8 times more frequent than in the no PTSD group (35 patients (20%); $p < 0.001$). This result was similar whether ketamine was administered on the battlefield (27 (28%) in the PTSD group vs. 14 (8%) in the no PTSD group; $p < 0.001$) or at the field hospital (44 (45%) in the PTSD group vs. 26 (15%) in the no PTSD group; $p < 0.001$). It should be noted that several patients received ketamine twice. Thus, among the war wounded who received ketamine, 54 out of 89 (61%) developed PTSD, whereas it was only 24% among the 185 patients who did not ($p < 0.001$).

The doses of ketamine administered (Fig. 2) were recorded for 193 patients on the battlefield and 63 at the field hospital, but simultaneously in only 50 patients. There was no difference between the mean (SD) doses of ketamine administered to the 32 patients in the PTSD group and the 18 patients in the no PTSD group (173 (144) mg vs. 209 (152) mg, respectively; $p = 0.42$).

Table 2 Overall comparisons between injured soldiers with post-traumatic stress disorder (PTSD) and without PTSD, according to bivariate analysis of 16 covariates. Values are mean (SD), number (proportion) or median (IQR [range]).

	n	PTSD n = 98	No PTSD n = 176	Ratio	p value
Age; years	253	30.0 (6.8)	28.6 (6.3)	-	0.10
Injury severity score	274	5 (3–13 [1–26])	3 (2–4 [1–6])	1.7	< 0.001
Glasgow coma scale	263	15 (15–15 [15–15])	15 (15–15 [15–15])	-	0.45
Blast injury	274	74 (76%)	115 (65%)	1.2	0.08
Associated fatality	274	21 (21%)	22 (13%)	1.7	0.05
Head injury	274	18 (18%)	10 (6%)	3.2	< 0.001
Traumatic amputation	274	6 (6%)	1 (1%)	11.0	< 0.01
Ketamine administered (battlefield)	210	27 (40%)	14 (10%)	4.1	< 0.001
Ketamine administered (field hospital)	253	44 (50%)	26 (16%)	3.2	< 0.001
Ketamine administered (both)	274	54 (55%)	35 (20%)	2.8	< 0.001
Midazolam administered (battlefield)	246	19 (24%)	7 (4%)	5.8	< 0.001
Morphine s.c. administered (battlefield)	204	21 (34%)	15 (11%)	3.2	< 0.001
Morphine i.v. administered (battlefield)	223	37 (51%)	21 (14%)	3.6	< 0.001
Morphine i.v. administered (field hospital)	253	51 (57%)	36 (22%)	2.6	< 0.001
Morphine administered (both)	263	59 (63%)	47 (28%)	2.3	< 0.001
Number of surgical procedures	274	1 (0–7 [0–13])	0 (0–1 [0–2])	5.6	< 0.001
Development of chronic pain	274	46 (47%)	33 (19%)	2.5	< 0.001
Development of physical, neurosensory or aesthetic sequelae	274	74 (76%)	83 (47%)	1.6	< 0.001

s.c., subcutaneous; i.v., intravenous.

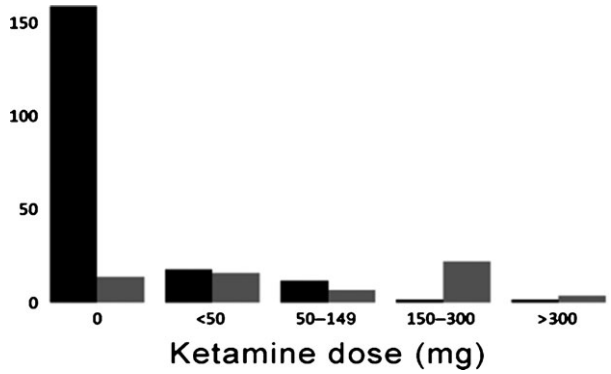

Figure 2 Distribution of ketamine dose according to number of administrations either on the battlefield (black shading) or at the field hospital (grey shading).

Covariates linked to the development of PTSD ($p < 0.1$) were introduced into a logistic regression model. To avoid colinearity, only global administration of ketamine and morphine was considered (battlefield and field hospital). In the analysis with all significant covariates, the only independent associations with PTSD development were the number of surgical procedures and development of ASD (Table 3). Administration of ketamine was not independently related to PTSD development. In the stepwise model, the same two covariates remained independently associated with PTSD development: ASD odds ratio (OR) (95%CI) 16.5 (6.5–41.8) ($p < 0.001$); and number of surgical procedures OR (95%CI) 1.4 (1.2–1.6) ($p < 0.001$) (Table 4).

Forty-one among 98 patients (42%) in the PTSD group experienced an ASD vs. only 8 (5%) among 176 in the no PTSD group ($p < 0.001$). Thus, an ASD predicted subsequent PTSD with 42% sensitivity and 95% specificity. Among the 50 patients who developed ASD for whom ketamine dose was simultaneously known for battlefield and field hospital, there was no difference between the mean (SD) ketamine doses given to the 11 ASD and 39 no ASD patients (226 (171) mg vs. 175 (139) mg, respectively ($p = 0.34$). The only ASD-related covariate was the development of PTSD. There was no independent association between ketamine administration and ASD development (Table 5).

Discussion

Medical practitioners in the French army commonly administer ketamine to injured patients on the battlefield, during surgical procedures and for postoperative analgesia. In this retrospective cohort study of 274 war-wounded soldiers with a prevalence of PTSD of 36%, ketamine administration was not independently associated with the occurrence of either ASD or subsequent PTSD.

Regarding the effects of ketamine in relation to psychological reactions to stress, scarce clinical evidence leads to conflicting results. Ketamine administered during stressful events may aggravate [3, 11, 12], prevent [7] or have no effect [8] on the subsequent development of PTSD. Since the first clinical experiments, the psychomimetic effect of ketamine has been

Table 3 Logistic regression for all included covariates (n = 263). Injury severity score (ISS) and number of surgical procedures were included as numeric values for each patient.

	Coefficient (SD)	p value	Odds ratio (95%CI)
Intercept	−2.00 (0.38)	< 0.001	-
Injury severity score	−0.02 (0.03)	0.45	0.98 (0.91–1.04)
Acute stress disorder	3.01 (0.49)	< 0.001	20.3 (7.7–53.4)
Blast injury	0.37 (0.36)	0.32	1.5 (0.7–2.9)
Head injury	1.01 (0.55)	0.06	2.8 (0.9–8.1)
Associated fatality	−0.17 (0.47)	0.72	0.9 (0.3–2.1)
Traumatic amputation	−0.30 (1.27)	0.81	0.7 (0.1–8.8)
Ketamine administration	1.06 (0.61)	0.08	2.9 (0.9–9.5)
Morphine administration	0.15 (0.59)	0.79	1.2 (0.4–3.8)
Total number of surgical procedures	0.22 (0.09)	0.02	1.2 (1.1–1.5)
Development of chronic pain	0.06 (0.45)	0.89	1.1 (0.4–2.7)
Development of physical, neurosensory or aesthetic sequelae	−0.18 (0.42)	0.67	0.8 (0.4–1.9)

The table includes ketamine and morphine administration on the battlefield and in the field hospital. When the model was tested with ketamine and morphine administered separately on battlefield and in the field hospital, neither ketamine nor morphine were independently linked to post-traumatic stress disorder occurrence.

Table 4 Results of stepwise logistic regression with post-traumatic stress disorder as the dependent variable.

	Coefficient (SD)	p value	Odds ratio (95%CI)
Intercept	−1.72 (0.21)	< 0.001	-
Acute stress disorder	2.81 (0.47)	< 0.001	16.5 (6.5–41.8)
Total number of surgical procedures	0.33 (0.07)	< 0.001	1.4 (1.2–1.6)

considered to be a problem [13]. In 1999, involvement of hyperglutamatergic states in the context of traumatic stress had been suspected; *N*-methyl-D-aspartate receptor antagonists (NMDA-R), which stimulate corticolimbic glutamate release, could be responsible for the dissociative symptoms associated with PTSD [14]. In a retrospective study of 56 trauma victims, Schönenberg et al. suggested that ketamine could have elicited PTSD symptoms [3] and later found a statistical link between ketamine and ASD [12], but without multivariate analysis. However, other studies have not validated these assumptions. Although ketamine may elicit dissociative symptoms, it also possesses an antidepressant activity [15] and, contrary to other antidepressants, acts within only a few hours. It has thus been proposed as a fast antidepressant for treatment-resistant depression, particularly in patients at high-risk of suicide [16]. Studies have demonstrated that besides its amnesic, anxiolytic [17] and antidepressant properties, ketamine is able to alleviate the symptoms of PTSD in both animals [17, 18] and humans [9].

McGhee et al. found that ketamine may protect burned soldiers from PTSD [7] although this was not confirmed in a later study involving a larger cohort [8]. Subanaesthetic doses of ketamine have not been shown to worsen dissociative symptoms in subjects with PTSD [19] and a randomised, controlled trial demonstrated that ketamine was superior to midazolam for reducing PTSD symptoms [9]. Moreover, recent case reports showed that ketamine, or other NMDA-R antagonists, far from exacerbating stress disorders, dramatically reduced them, at least transiently [20–24]. Experimentally, when given immediately after a psychological stressor, ketamine prevented synaptic transmission from prefrontal cortex to amygdala [25]. Several mechanisms have been advocated; the most interesting among them may be NMDA-R inhibition [26] with glutamatergic stimulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors located upon GABAergic interneurons [27], up-regulation of brain-derived neurotrophic factor [28] or intracellular targets such as activation of mammalian target of rapamycin pathway (m-TOR) and subsequent synaptogenesis. Thus, ketamine modulates neurotransmitter concentration, synaptic activity, cerebral plasticity and reconfiguration of cortical networks, especially in the anterior cingulate and prefrontal cortices [18, 29]. By restoring the correct balance between detrimental and protective inputs from the amygdala to the medial prefrontal cortex [30], 'prophylactic'

Table 5 Results of logistic regression with acute stress disorder (ASD) as the dependent variable.

	Coefficient (SD)	p value	Odds ratio (95%CI)
Intercept	−4.14 (0.66)	< 0.001	-
Injury severity score	0.0006 (0.04)	0.98	1.0 (0.9–1.1)
Associated fatality	1.49 (0.86)	0.08	4.4 (0.8–23.8)
Traumatic amputation	1.24 (1.23)	0.31	3.5 (0.3–38.6)
Ketamine administration	−0.52 (1.15)	0.65	0.6 (0.1–5.7)
Midazolam administration	0.09 (1.11)	0.93	1.1 (0.1–9.7)
Morphine administration	−0.35 (1.02)	0.73	0.7 (0.1–5.2)
Development of chronic pain	−1.53 (0.84)	0.07	0.2 (0.4–1.1)
Development of physical, neurosensory or aesthetic sequelae	1.27 (0.65)	0.052	3.6 (0.9–12.9)
Post-traumatic stress disorder	3.58 (0.68)	< 0.001	35.8 (9.4–136.4)

Injury severity score and number of surgical procedures were included as numeric values for each patient. Drug administration has been considered only for initial forward step of management (on battlefield).

ketamine may be able to elicit an actual 'resilience to stress' [31] and prevent subsequent PTSD [32].

Concerning the real-life setting, few series have been published. The main strength of our study is a long post-event observation period. The diagnosis was assessed at least 3 months after the traumatic event and consolidated with a 2-year observation period. Using these strict criteria, we found a PTSD incidence of 35.8%, which is 10% higher than in the study by McGee et al. [7]. However, the diagnosis of PTSD in our study was made by a psychiatrist rather than a checklist and took place later in relation to the traumatic event; the diagnosis of PTSD is much more likely at 3–6 months following the traumatic event.

The relationship between ketamine administration and trauma severity explains the confounding fact that patients in the PTSD group received three times more ketamine than those in the no PTSD group. Indeed, the multivariate analysis showed no significant difference in the incidence of PTSD between soldiers who received ketamine and those who did not. In addition, PTSD development was only related to ASD and total number of surgical procedures; these combine the composite effects of initial trauma severity (associated fatality, ISS, blast injury) and the sequelae of the injury, including the development of chronic pain.

There are some limitations to our study. First, like other published studies, our study suffers from its retrospective design. A randomised, controlled trial to decide whether ketamine is able to prevent PTSD in wounded soldiers is obviously impractical in the context of war. Second, although our study consisted of a large cohort, it may not be adequately powered for the primary end-point. However, our cohort is similar in size to other published work; Schönenberg et al. studied fewer patients (n = 56) [3]. The two studies by McGhee et al. included 147 and 289 patients, respectively [7, 8], but included imprecise timing of PTSD diagnosis. Finally, we only obtained a limited number of precise ketamine doses, which may influence the effects of the drug.

The use of ketamine use has increased over the last 15 years. Whether it has the potential to be able to prevent PTSD development when used for war-related injuries will be debated until a randomised, controlled trial is available. For the moment, our study suggests that ketamine administration in the traumatic military setting does not have a detrimental effect in terms of the development of acute and chronic stress disorders.

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