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General

'The Drug of War' - a historical review of the use of Ketamine in military conflicts

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Abstract

Anaesthesia for surgery during armed conflict was traditionally based on simple and reliable techniques. These often required a minimum of equipment and drugs while ensuring rapid and safe patient recovery. Ketamine, which first became available in Britain in the 1970s, was thought to offer certain favorable characteristics for use as a military anaesthetic agent. This article discusses the use of ketamine in many of the major armed conflicts that have occurred since its introduction. It also catalogues the methods used by anaesthetists at the time and their opinions of the drug's success.

Anaesthesia and surgery have taken place on the battlefield under difficult and stressful conditions, often with basic equipment and resources. Any armed conflict has the potential for mass casualties who will require surgery by a limited number of staff (1). In modern military conflicts, patients may require more than one anaesthetic for debridement or delayed primary suture of their wounds (2). This is particularly pertinent with the central protection offered by modern combat body armor resulting in soldiers surviving with peripheral injuries. In order to maintain an efficient throughput of injured personnel, patients must be able to recover quickly from the effects of the anaesthetic agents and be able to maintain a clear airway as soon as possible (1). A prolonged recovery period has the potential to delay surgery on further casualties and place additional demands on the recovery staff (3). Anaesthesia in a military conflict therefore must be based, at least in the initial phases, on reliable and simple techniques that require a minimum of equipment and drugs, and that ensure a rapid and safe recovery (1).

Phencyclidine was introduced into clinical practice in 1958 and although it proved a useful anaesthetic agent, it was associated with such severe adverse psychological effects in the recovery period that its use was soon abandoned (4). Ketamine, then named C1581, was one of the 200 phencyclidine derivatives that were investigated for clinical purposes. It underwent animal testing in 1962 and subsequent pharmacological studies in early 1964 (5-7). The first human administration was by Dr Guenter Corssen in August 1966 (8) and the effects and findings were subsequently reported in the *Journal of Anesthesia & Analgesia* later that year (9). This led to ketamine first becoming available in Britain for clinical trials in the January of 1970, but early evaluations reported a high incidence of delirium and unpleasant dreams during the recovery period (10). Even as early as 1971 it was commented in the literature that the use of ketamine, despite its ease of administration, *'must be restricted to physicians skilled in the management of airway problems'* (11).

In June 1970 a conflict erupted between the Palestine Liberation Army and the Jordanian Army and although a cease-fire was rapidly negotiated, the situation escalated once more on the 17th September 1970. Casualties increased in the Jordanian capital Amman and on 19th September King Hussein made an appeal to the British, French and American Governments for medical aid. Wounded casualties were lying in the streets as hospitals became overwhelmed and the number of injured rose to within the region of five thousand. A composite medical team, code-named *'Ferrie Force'*, was dispatched from the UK to Cyprus on 21st September 1970. This unit consisted of a 50-bedded element of the No. 2 Field Hospital, the 50th Field Surgical Team, Hygiene, Field Ambulance and Signals detachments. The British Field Hospital arrived in Amman on 30th September 1970 and subsequently described their work in the *Annals of the Royal College of Surgeons* (12), a summary of which is given below.

The use of ketamine (*or Ketalar as it was known as at the time*) was said to produce a '*form of dissociative anaesthesia*' and also provided '*a reasonable degree of analgesia*' as it was employed in the treatment of burns victims. Many of these casualties were young children who understandably found the procedures frightening and painful. A dose of 10 $mg.kg^{-1}$ of ketamine was administered intramuscularly and allowed a treatment time of 30-50 minutes before there were signs of discomfort (12). Intramuscular ketamine was also used for changing the burns dressing in children and was described as '*placing the child in a trance-like state for about 20 minutes*' and this generally allowed the nurses sufficient time to complete their duties. In total, 230 general anaesthetics were administered by the field hospital team and ketamine was given 51 times to 22 different patients, being used as the sole anaesthetic agent on 33 occasions. Anaesthetists used ketamine via the intramuscular route in the majority of cases and a dose of 10 $mg.kg^{-1}$ was administered with occasional supplementations of 2-3 $mg.kg^{-1}$ intravenously. The absence of accessible veins in many of the burns patients made the intramuscular route invaluable and Ketamine was well suited to administration in this way. From a surgical point of view, occasional limb movement was noted to occur in a few patients, as was increased muscle tone, although this did not seem to interfere with surgery. A premedication of atropine was given to all patients receiving ketamine and this appeared to reduce salivation (12).

Regarding the other properties of ketamine, the advantage of patients retaining their laryngeal reflexes was noted, respiratory exchange was reported to be adequate and patients were able to maintain their own airway. In a busy environment this allowed the nursing staff to look after some of the patients, particularly those undergoing burns treatment, without a supervising anaesthetist, who was free to deal with more urgent tasks. This was a very favorable attribute in a military environment. Postoperatively there were very few undesirable affects reported although two patients suffered what was described as '*severe vomiting*' and an 11 year old child became confused and experienced '*bad dreams*'. These complications were controlled by intravenous diazepam at a dose of 0.3-0.5 $mg.kg^{-1}$ as this had been described previously in the literature (13) and patients were generally allowed to recover undisturbed. We now know that ketamine is the only anaesthetic agent available which has analgesic, hypnotic and amnesic effects and that it produces a state of 'dissociative anaesthesia' which results in electrophysiological dissociation between the limbic and cortical systems (14).

Mass casualties in a war zone can lead to a shortage of resources and surgeons were keen to have an anaesthetic agent at their disposal that they could administer themselves. This would allow their anaesthetic colleagues to concentrate on other, more important duties. A review in 1970 by Phillips and colleagues (15) proposed that an ideal agent for the 'surgeon-anaesthetist' should be able to '*leave the surgeon free to forget about the patient's general condition and airway whilst he concentrates on the surgery*'. A rapid recovery '*free from any special nursing requirements*' was also desirable. The intravenous administration of ketamine '*proved disappointing'* and was found to be unreliable in producing anaesthesia. In their view, ketamine provided such a short analgesic time that patients ended up requiring constant attention instead of reducing the clinical input as was expected. Ketamine was also noted to cause marked increases in blood pressure and casualties experienced distressing hallucinations.

Intramuscular ketamine in contrast was more reliable and patients were free from hypertensive effects and hallucinatory phenomena, although a disadvantage was a prolonged recovery time. In the series of patients reviewed, '*the average time from the last dose of the drug to accessibility* (not defined) *was 122 minutes*', which was deemed impractical in a military setting. They concluded that ketamine could be recommended as the anaesthetic of choice in remote hospitals and to lone medical officer stations but that the indications for its use in larger and better staffed establishments were *'less obvious'*.

British Army anaesthetists reported their work as part of the field surgical team supporting counterinsurgency operations in Oman over a 32 month period in 1972 (16). Ketamine was used for the daily dressing changes of a mine (blast) victim. This time there was a less favorable report as ketamine seemed to result in hallucinations and as a consequence was abandoned and replaced by pethidine and diazepam. The authors however reported that it had been useful in another patient requiring the same treatment without complications.

The literature is replete with anecdotal case reports of ketamine use by anaesthetists working in the various war zones during subsequent years and some of these are summarized in Table 1.

Table 1 – A summary of the use of Ketamine through Military Conflicts

Reference	Conflict/ Study	Main conclusions
(17)	Yom Kippur War, 1975	Series of 51 patients. Ketamine caused a *'catatonic schizophrenic-like stupor with loss of response to painful stimuli'*. Favorable effects on the cardiovascular system with an increase in cardiac output
(18)	Afghanistan, 1983	Intra muscular Ketamine *'adequate, safe, and easy to administer'* for patients requiring amputation to damaged limbs caused by the pencil mines *'even in a race of people who were known to express their emotions so strongly'.*
(22)	Fighting on the Thai-Cambodian border, 1984	Study involving 17 men and 1 woman injured by land mines. Ketamine would have a substantial advantage over pentazocine in patients suffering from shock or respiratory impairment and recommended for use at the scene of an accident or *'whenever a difficult transfer to hospital is anticipated'.*
(23).	Study - Intrathecal ketamine to obtain surgical analgesia, 1984	As a single agent, ketamine did not produce motor block. The addition of adrenaline caused a complete motor block, which persisted for the same duration as surgical analgesia. Intrathecal ketamine could provide analgesia of sufficient intensity to allow surgery, without interfering with cardiovascular or respiratory function.
(1).	Study: The effect of heavy papaveretum premedication and Althesin induction on the incidence of emergence phenomena,1984.	Ketamine *'did not fulfill its apparent potential'.* Adequate anaesthesia could not be guaranteed and there was a high incidence of side effects.

Reference	Conflict/ Study	Main conclusions
(24)	Case series: 206 Asian adult patients anaesthetised with ketamine under field conditions, 1985	Administering ketamine as an infusion *'was much more satisfactory'* than intermittent boluses. Less than 1 $mg.kg^{-1}$ of ketamine was required for induction. The total dose administered was less than that required in a repeated bolus method.
(25)	Study: Ketamine, midazolam and vecuronium, delivered intravenously to the patient via a syringe pump, 1988.	100 ASA I-II patients, aged between 16 and 50 years underwent elective abdominal, thoracic or body surface surgery. Concluded that this technique was advantageous when inhalational agents were either not available or were not suitable and was *'simple, effective (and) versatile'.*
(27)	Desert Anaesthesia Symposium, January 1991	The infusion rate of mixture described in [27] should be reduced by one third after one hour and stopped 10 minutes before the end of surgery. Extubationwas possible between 2 - 3 minutes and the patients were awake and able to correctly answer questions between 22 - 29 minutes.
(26)	Gulf War, 1992.	Modification of technique described in [27] to a rapid sequence induction using suxamethonium bromide. Description of two patients undergoing extensive debridement following trauma with anaesthetic times of 111 and 113 minutes. Ketamine produced hypotension in 10% on induction of anaesthesia.
(28)	Kitgum Government Hospital in North Uganda in 1999	Ketamine was a useful agent when an induction dose was administered and a maintenance infusion of 10-20$mcg.kg.min^{-1}$ maintained in combination with a premedication of diazepam, glycopyrrolate and a local anaesthetic block.

In 1982, anaesthetists serving with the British forces administered ketamine during the Falklands campaign. HMS Hermes, one of the Royal Navy's aircraft carriers, was tasked to treat casualties from the warships and auxiliaries of the battle group and to provide a routine hospital service for the smaller ships. EXOCET missile attacks on HMS SHEFFIELD and HMS GLAMORGAN resulted in 11 sailors who required general anaesthesia but only one patient with 60% burns and shrapnel injuries presented problems (not stated) for the serving anaesthetists (19). Techniques involving droperidol and ketamine to facilitate wound debridement and burn dressing changes were employed. The use of ketamine to aid dressing change was becoming very popular, particularly due to the many burns victims that resulted from modern warfare.

On the 9th of June 1982, 150 patients were admitted to the hospital ship SS UGANDA as a result of the bombings of the landing ships Sir GALAHAD and Sir TRISTRAM (19). 10% of these casualties required surgery within 2 hours of admission and, as most of the anaesthetics given ashore had included halothane, this was usually avoided as an anaesthetic agent on board. This therefore favored the use of ketamine which was employed in 50 cases, usually in combination with diazepam. Interestingly on this occasion emergence phenomena was not a problem.

Whilst working in the field, British Army Anaesthetist Major MD Jowitt developed a technique using ketamine as his induction and analgesic agent, to cause *'sleep and intensive analgesia'* at the start of operations (20). He then used increments of ketamine to provide additional analgesia, with diazepam being given towards the end of the procedure. If the surgery was expected to last more than twenty minutes, casualties were induced with Ketamine and then had their anaesthetic maintained with Halothane and Trichloroethylene via the Triservice Apparatus (21). Pethidine was also used to provide additional analgesia. Major Jowitt considered the ketamine / diazepam combination to be adequate for those short cases that did not involve body cavity surgery. He felt that there were several advantages of a total intravenous technique that included *'simplicity, a rapid onset of dissociative hypnosis, adequate analgesia, a relatively safe airway and an acceptable recovery'*. In view of the psychological side effects of ketamine that had been described previously, patients were interviewed postoperatively concentrating on whether they had had nightmares or unpleasant dreams, but no adverse comments were recorded. In this instance, ketamine was considered as good as thiopentone as an induction agent.

Other reports from the Falklands Campaign (3) described anaesthesia being induced intravenously with either 2 $mg.kg^{-1}$ ketamine or a *'sleep dose'* of sodium thiopentone and a dose of 300mcg of atropine was usually administered. Ketamine received favorable reports as even though it did not always increase pulse and blood pressure in the severely shocked patient, it rarely caused cardiovascular depression. Slow injections did not result in respiratory depression and there was a rapid onset of hypnosis and 'intense analgesia'. Interestingly, it was commented that *'the initial and frequently turbulent period of anaesthesia between intravenous induction and the volatile agents attaining their minimal alveolar concentrations (MAC) could be covered with the use of ketamine'.* In contrast to other authors, the dissociative anaesthesia with ketamine and diazepam *'proved to be of tremendous value for a number of short cases not involving body cavities'.* There were also favorable recovery times and the usual emergence phenomena were not reported.

As discussed, ketamine has been associated with psychomatic effects leading to concerns that it may increase the risk of post-traumatic stress disorder (PTSD). Recently, an American Military study (29) addressed this by investigating the prevalence of PTSD in American troops with burns injuries returning from conflict in the Middle East. They concluded that the use of ketamine may actually decrease the prevalence of PTSD in the combat-burned patient. Explanations for this finding included the better pain management received by those administered ketamine, the neuronal protection provided by ketamine, and antagonism of the N-methyl-D-aspartate (NMDA) receptor.

Ketamine has also been considered in a recent review to be an ideal drug for use in many pre-hospital situations (30) with experience again suggesting that it is *'safe, effective, and may be more appropriate than drugs currently used by pre-hospital providers'*. This will be of interest to military anaesthetists who are involved in care of casualties forward of the traditional Role 3 field hospital. Despite negative comments, ketamine has been a very useful drug since its discovery and licensing in the early 1970s and is still used by many military anaesthetists today. Recently, controversies surrounding the use of ketamine in head injured patients have been re-addressed and it has also been suggested that as a very rational choice for rapid sequence induction in haemodynamically compromised patients (31). We await the reports of ongoing and future conflicts to see if ketamine continues to serve well as the anaesthetists 'drug of war'.

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