

# The Possible Effect of Acute Suicidal Tramadol Overdose on CD4+ Percent

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## Abstract

**Background:** Opioids can produce several well-known adverse events, and recently has been recognized to interfere with the immune response. However, from several studies it emerges that not all opioids induce the same immune-suppressive effects, some opioids have little effect on immunity, others can be immune-suppressive or immune-stimulant. Evaluating each opioids profile is important for appropriate analgesic selection. Analgesic drugs devoid of immune-suppressive effects might offer a good alternative to morphine for the treatment of postoperative pain.

**Aim:** This study aimed to evaluate the effect of tramadol on immune system by measuring CD4+ percent in patients presented with acute suicidal tramadol overdose.

**Methods:** This study included 40 candidates divided into 2 groups, tramadol group consisting of 30 patients with acute suicidal tramadol overdose and control group consisting of 10 healthy non-smoker persons. Lymphocytes % and Expression of CD 4+ % were assessed after admission to detect effect on immunity.

**Results:** The results revealed that there is significant decrease in the lymphocytic percent and CD4+ expression in the tramadol group.

**Conclusion:** We can conclude that tramadol overdose had suppressive effect on lymphocyte proliferation and CD4 expression and other studies are needed to test the effect of different doses of tramadol on immunity to document its safety as analgesic in immune-compromised patients.

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## Introduction

Recent studies suggest that opioids can have an adverse impact on the immune system and opioids use and abuse has been linked to significant immune-suppression, which renders individuals susceptible to infection. A variety of mechanisms have been proposed to explain how opioids suppress the immune system. Modulation of the inflammatory response appears to be a target of these compounds, including effects on phagocytic activity and response of cells to various chemo-attractant molecules, also opioids treatment has an impact on antibody responses through modulation of both cytokines and cytokine receptor expression (Liu et al., 2008).

Moreover several studies found that morphine can decrease the effectiveness of several functions of both natural and adaptive immunity, and significantly

reduces cellular immunity leading to increased morbidity and mortality due to infection (Wang et al., 2008).

However, it emerges that not all opioids induce the same immune-suppressive effects, and evaluating each opioid profile is important for appropriate analgesic selection (Sacerdote, 2006).

Tramadol is a synthetic opioid analgesic, it is commonly prescribed for moderate to severe pain and became abused, more popular among teens, in most countries (McKeon et al., 2011). Tramadol provides analgesia through 3 mechanisms: mu-opioid binding, serotonin reuptake inhibition and nor-epinephrine reuptake inhibition (Sansone and Sansone, 2009). It has been claimed that, in contrast to most opioids, tramadol does not suppress immune functions.

## Aim of the work

The aim of this study is evaluate the effect of tramadol on immune system by measuring CD4+ percent in patients presented with acute suicidal tramadol overdose to the Poison Control Centre (PCC), Ain Shams University Hospitals.

## Patients and methods

### Type of the study

Prospective Randomized Clinical Trial (RCT), conducted in Poison Control Centre, Ain Shams University Hospitals, Cairo.

### Type of participates

the study involved 2 groups : (tramadol group ) included 30 patients with acute suicidal tramadol overdose presented to the Poison Control Centre (PCC), Ain Shams University Hospitals from period of 1/1/2014 - 30/5/2014. All patients were presented with coma with history of acute suicidal ingestion of 2-3gram tramadol tablet (tablet 225mg - not their own treatment). (Control group) included 10 healthy non-smoker volunteer.

### Exclusion criteria

Patients presented with sepsis, shock, drug abuse, opiate intake, history of alcoholic intake, chronic illness or hepatitis were excluded from the study due to the possible effect of these diseases on immunity.

### Biochemical parameters

Blood samples were taken after admission for assay of lymphocytic percent and CD4 percent. Also serum hepatitis B surface antigen (HBV S Ag), hepatitis C antibodies (HCV AB) and human immune deficiency virus antibodies (HIV AB) were done on admission to exclude positive cases from the study.

Urine samples were taken after admission for tramadol and opiate screen to prove the tramadol cases and exclude the opiate cases from the study.

- I. Expressions of CD4+ in blood samples were measured as percentages of total lymphocytes by flow cytometer (FACS, BD, United States) by obtaining 3 ml blood samples of each patient from non-infused median cubital vein and keeping it in an EDTA-anti-coagulation tube (Becton- Dickinson, Heidelberg, Germany); incubating the blood with CD4+ monoclonal antibodies (BD, United States) at 25 C° for 30

minutes; lysing erythrocytes with hemolysin (BD, America; and diluted with distilled water at the ratio 1 : 9) for 10 minutes then centrifuging it at 1100 rpm (revolutions per minute) for 5 minutes; removing the supernatant, washing the cells with phosphate-buffered saline solution (PBS) 2 ml then centrifuging it at 1100 rpm for 5 minutes; removing the supernatant, adding 1% formamint-satured PBS to float blood cells then keeping it at 4 C° without light for 2–4 hours; using flow cytometry to measure the expressions of CD4+ as the percentages of total lymphocytes.

- II. Hepatitis C antibodies, hepatitis B surface antigen and human immune deficiency virus test done by ELISA using Elisa kits.
- III. Tramadol and opiate detection was done by capillary gas chromatography using DANI GC 1000 made in Italy ( Shung-Tai et al. 1999).

The Ethics Committee approved the protocol of this trial. Relatives of recruited patients provided written informed consent for participation.

Statistical analysis:

The data was analyzed using SPSS statistical software (11.5.0; SPSS Inc., Chicago, IL). Differences between both groups were tested using student (t) test. A p value < 0.05 is considered statistically significant.

## Results

Thirty patients with acute suicidal tramadol overdose were taken up for the study and 10 healthy people were taken as a control. (Table 1) shows that the mean lymphocyte percent (%) for the tramadol group was  $9.6 \pm 2.9$ , while the mean lymphocyte % for the control group was  $29.4 \pm 7.1$  and there is significant decrease in the total lymphocyte percent in the tramadol group when compared with the control group with P value 0.0001. (Table 2) shows that the mean CD4% for the tramadol group was  $28.6 \pm 9.3$ , while the mean CD4 % for the control group was  $39.3 \pm 6.3$  and there is significant decrease in the CD4% in the tramadol group with P value 0.004. (Table 3) shows that HBV SAg, HCV AB, HIV AB and opiate screen were negative in the tramadol and control groups and tramadol screen was positive in the tramadol group.

**Table (1): Student (t) test of Lymphocyte % comparing between tramadol group and control group:**

Lymphocyte %	Tramadol group No = 30	Control group No = 10
mean	9.6	29.4
SD	2.9	7.1
P value	0.0001*	

*P < 0.05 significant*

**Table (2): Student (t) test of CD4 % comparing between tramadol group and control group:**

CD4 %	Tramadol group No = 30	Control group No = 10
mean	28.6	39.3
SD	9.3	6.3
P value	0.004*	

*P < 0.05 significant*

**Table (3) Results of HBV S Ag, HCV AB, HIV AB, Urine tramadol and Urine opiate in the tramadol and control groups:**

	Tramadol group No = 30	Control group No = 10
HBVS Ag	+ve = 0 -ve = 30	+ve = 0 -ve = 10
HCV AB	+ve = 0 -ve = 30	+ve = 0 -ve = 10
HIV AB	+ve = 0 -ve = 30	+ve = 0 -ve = 10
Urine tramadol	+ve = 30 -ve = 0	+ve = 0 -ve = 10
Urine opiate	+ve = 0 -ve = 30	+ve = 0 -ve = 10

*+ve = positive, -ve = negative*

## Discussion

Tramadol use and abuse became more popular in most countries. Being an opioid, tramadol carries all possible risks known from other opiates (Adams et al., 2006). Opioids have different effects on immunity via direct actions on neutrophils, monocytes, natural killer (NK) and T cells (Boland et al., 2013).

The inhibitory effect of opioids on phagocytic cell capacity is well established. However, the effect of synthetic opioids on this aspect of cell function is controversial. Our results of studying 30 patients with acute suicidal tramadol overdose revealed significant decrease in the lymphocyte percent and CD4 expression in the tramadol group when compared with the control group.

Similarly Wang et al., 2006 studied 45 patients undergoing elective gastric cancer surgeries under general anaesthesia, they randomly allocated into 3 groups. Group I received morphine after surgery, group II using tramadol, and group III using tramadol with lornoxicam. Expressions of CD3, CD4, CD8, were measured as percentages of total lymphocytes and they found that using combination of lornoxicam with tramadol has the same good analgesic efficacy and less immunity depression than using morphine or tramadol.

Also Qian et al., 2005 found that suppression of immunity due to tramadol was dose dependant where they studied 20 outpatients without any immune diseases; their peripheral blood was collected and pre-treated with different concentrations of morphine or tramadol for 48 h, while the control group received neither. He found remarkable Th2 (T helper 2) differentiation after pre-

treatment with morphine or tramadol. IL-4 and IL-10 elevated significantly while IL-2 and IFN- $\gamma$  decreased significantly compared with control groups. They also found that the suppression of cell-mediated immunity was dose dependent and Th2 differentiation was closely associated with the levels of cytokines, which was the cause of the immune alteration. It indicates that excessively high concentration of these drugs should be avoided in clinical applications in order to maintain a healthy Th1/Th2 balance. Also they said that both morphine and tramadol could direct human T-helper cell into Th2.

In contrast Zhou et al., 2013 in their prospective randomized controlled trial on 30 patients undergoing elective gastric cancer surgeries observe the effect of tramadol on T-lymphocyte subsets (CD3+, CD4+, CD8+) and natural killer (NK) cells.

They found that tramadol in therapeutic dose can reduce the decrease of T-lymphocytes subsets and NK cells that found due to gastric cancer and stress of the operation, thus improve the cellular immune function in the peri-operation of gastric cancer.

Moreover Mostafa et al., 2012 performed a study on 70 patients complaining of cancer related pain to evaluate effect of morphine versus tramadol on the immune response during management of patients with chronic cancer pain. They found that, the concentration of IL-2 and INF  $\gamma$  in the serum of patients in morphine group was decreased significantly than that in the pre-treatment phase while increased in the tramadol group than the pre-treatment phase and these changes were

statistically significant. Both IL-2 and INF  $\gamma$  were significantly higher in tramadol group than morphine group along studied periods.

Also Shirzad et al., 2009 studied the effects of tramadol in comparison to morphine, on the number of mouse peritoneal phagocyte.

Ten days after the start of drug administration, the number of phagocytes reduced in morphine group ( $P < 0.05$ ), and enhanced in tramadol group ( $P < 0.05$ ) and they concluded that tramadol stimulation of immune system may offer a good alternative to morphine for the treatment of patients in whom immune-suppression might be hazardous or in patients who cannot tolerate the side effects of morphine. In another way Barkin 2008 found that increasing serotonin and nor epinephrine reduce inflammatory cytokines which are released by the brain in response to stress.

The inflammatory cytokines would have slowed recovery from a workout or illness impairing one's immune system and healing, also the increase of serotonergic tone has usually been associated with stimulation of NK activity and lymphocyte proliferation thus tramadol may have an anti-inflammatory effect. Moreover Beilin et al., 2005 studied healthy volunteers, where peripheral blood polymorphonuclear cells and monocytes were incubated with tramadol, or with morphine.

After incubation for 60 minutes the percentage of cells engulfing latex particles and the phagocytic index (number of particles phagocytized by each individual cell) were detected. They found that tramadol did not affect neither the percentage of cells phagocytizing latex particles, nor the phagocytic index of both polymorphonuclear cells and monocytes. On the other hand, morphine caused significant decrease in phagocytosis of monocytes phagocytizing latex particles and decrease in the monocyte phagocytizing index.

They concluded that the lack of noxious effect of tramadol on the engulfing capacity of phagocytic cells suggests additional benefit to the relatively safe profile of the drug.

Our explanation for the confliction between our results and the opposing opinion, that we studied the effect of larger doses of tramadol on CD4 % (as a marker of immunity), while they were using therapeutic dose of tramadol in their studies. So we warn about using higher dosage of tramadol in management of pain (especially due to rapid tolerance effect) because it may had reverse effect on immunity similar to other opioids.

## Conclusion

We can conclude that tramadol overdose had a suppressive effect on lymphocyte proliferation and CD4 expression.

## Recommendations

Further studies needed to test the effect of different doses of tramadol on immunity to document its safety as analgesic in immune-compromised patients.

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### الملخص العربي

## التأثير المحتمل لحالات الجرعة الزائدة الانتحارية الحادة للترامادول على نسبة CD4+ المنوية

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**الخلفية:** يمكن أن تنتج المواد الأفيونية العديد من الأحداث السلبية المعروفة، ومؤخراً تم الاعتراف بدورها في التدخل في الاستجابة المناعية. ومع ذلك يتضح من عدة دراسات أنه ليست كل المواد الأفيونية تحدث نفس التأثيرات المثبطة للمناعة، فبعض المواد الأفيونية لها تأثير لا يذكر على المناعة و المواد الأخرى قد تكون مثبطة أو محفزة للمناعة. لذا فإن تقييم كل مركب أفيوني على حدة امر هام لاختيار المسكن المناسب، حيث أن العقاقير المسكنة الخالية من الآثار المثبطة للمناعة قد تقدم بديلاً جيداً للمورفين لعلاج آلام ما بعد الجراحة.

**الهدف:** هدفت هذه الدراسة إلى تقييم تأثير الترامادول على الجهاز المناعي عن طريق فحص مرضى مركز علاج التسمم المنتحرين بجرعة زائدة من الترامادول.

**الأساليب:** اشتملت هذه الدراسة على ٤٠ فرداً تم تقسيمهم إلى مجموعتين، مجموعة الترامادول و تشمل ٣٠ مريضاً بسبب جرعة زائدة من الترامادول والمجموعة الضابطة و تشمل ١٠ أشخاص أصحاء غير مدخنين. تم تقييم نسبة الليمفوسيت و سي دي ٤ بعد الدخول للكشف عن التأثير على المناعة.

**النتائج:** أظهرت النتائج أن هناك انخفاضاً ذا دلالة احصائية في نسبة الليمفوسيت و سي دي ٤ في مجموعة الترامادول .

**الخلاصة:** ويمكننا أن نستنتج أن الجرعة الزائدة من عقار الترامادول لها تأثير مثبط على نسبة الخلايا اللمفاوية و نسبة السي دي ٤ المنوية و ان مطلوب دراسات اخرى لتقييم تأثير الجرعات المختلفة من الترامادول على المناعة لتأكيد امان استخدامه كمسكن في حالات المناعة المختلة.

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