The Effect of Propranolol on Posttraumatic Stress Disorder in Burned Service Members

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Posttraumatic stress disorder (PTSD) is reported to affect almost one third of the civilian burn patient population. Predisposing factors for PTSD include experiencing a traumatic event. Of Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) soldiers returning home after deployment without injury, 17% reported cognitive symptoms of PTSD. The authors recent study of soldiers burned in OIF/OEF showed a PTSD prevalence of ~30%, which is similar to civilian studies. Burns are characterized by hypermetabolism and increased catecholamine levels. β-Adrenergic receptor blocking agents, like propranolol, decrease catecholamine levels. Propranolol may reduce consolidation of memory and a prophylaxis for PTSD. This retrospective study examines the relationship between PTSD prevalence and propranolol administration. After institutional review board approval, propranolol received, number of surgeries, anesthetic/analgesic regimen, TBSA burned, and injury severity score were collected from patients charts. The military burn center received 603 soldiers injured in OIF/OEF, of which 226 completed the PTSD Checklist-Military. Thirty-one soldiers received propranolol and 34 matched soldiers did not. In propranolol patients, the prevalence of PTSD was 32.3% vs 26.5% in those not receiving propranolol ($P = .785$). These data suggest propranolol does not decrease PTSD development in burned soldiers. The prevalence of PTSD in patients receiving propranolol is the same as those not receiving propranolol. More research is needed to determine the relationship between PTSD and propranolol.
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Burn injuries are characterized by hypermetabolism resulting in increased catecholamine levels and muscle catabolism, loss of lean muscle mass, which is extremely detrimental to patients who are often bedridden by their injuries and may not be able to do weight-bearing exercise. To treat or prevent muscle catabolism, β-adrenergic receptor blocking agents, such as propranolol, are given to decrease catecholamine levels and the hypermetabolic response.

Up to 17% of noninjured veterans (no combat injury) returning from Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) report cognitive and psychological symptoms consistent with posttraumatic stress disorder (PTSD).[1–6] PTSD is a psychological disorder characterized by recurrent flashbacks, nightmares, emotional disturbances, social withdrawal, and forgetfulness. It often arises after a traumatic experience in which the participant is threatened with harm or death. Predisposing factors for PTSD include experiencing a traumatic event, threat of injury or death, and threat to one's own physical integrity, such as untreated pain.[7,8] The risk of PTSD increases if the participant is physically harmed.

PTSD has been reported to affect almost one third of the burn patient population, with civilian burn centers reporting a range of 8 to 45%[9–12] depending on the timing of the screening tool and the diagnostic tool used. Recent studies have suggested that burn size is not a good predictor of PTSD development,

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but that the level of social support the patient perceives that he or she has is a good predictor.[12,13] In addition, PTSD at 1 month, 6 months, 12 months, and 24 months in burn patient can be predicted by high distress on the acute stress disorder screenings.[12,14,15]

PTSD is based on memory of a traumatic event. Memory can be distinguished as short term or long term. Short-term memories last for seconds to minutes whereas long-term memories last for days, weeks, years, or even a lifetime. Short-term memory becomes long-term memory by a process known as consolidation, which transforms newly learned information to stable modifications. Memory consolidation is dependent on the cAMP response element binding protein transcriptional pathway that is activated by multiple receptors including the *N*-methyl-D-aspartate receptors, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors, and adrenergic receptors. During the initial phase of consolidation, the memory is unstable and can be disrupted by trauma, other learning, seizure, or administration of drugs such as protein and RNA synthesis inhibitors. Once the consolidation process is complete, memories are stable and insensitive to these interrupting factors. Established memories can become sensitive again through reactivation and can be disrupted by administration of noradrenergic blockers.

PTSD prophylactic agents, including β-blockers which prevent memory reconsolidation, are frequently given to patients who were exposed to traumatic effects to prevent PTSD development.[16–20] One commonly used β-blocker, propranolol, is known to disrupt memory reconsolidation through antagonism of the β-adrenergic receptor itself. In a study that examined the noradrenergic blockage following reactivation of fear memory in rats, the memory impairing effects of propranolol were greater when propranolol was administered after memory reactivation rather than immediately after the initial training.[19] Timing is critical to this effect; waiting too long after memory reactivation abrogated this effect. This suggests that memory reactivation triggers a β-adrenergic receptor-dependent cascade of intracellular events. Propranolol impaired reconsolidation of memories, but had no effect on memory without reactivation.[17] However, one of the side effects of propranolol is sleep disruption and sedation.[21,22]

This study examined the effect of propranolol administration on the prevalence of PTSD in burned soldiers and to investigate whether propranolol usage can predict PTSD development in models. This study also examined the association of propranolol and intensity of memories of the traumatic event.

METHODS

The study population included U.S. military soldiers who had sustained thermal injuries during OIF/OEF deployments, and who were cared for at the military burn center between 2002 and 2007. This study investigated the prevalence of PTSD in burn patients receiving propranolol compared with those not receiving propranolol. Timing and dose were not considered.

Inclusion criteria for this study required that the patient have been screened for PTSD using the PTSD Checklist-Military (PCL-M) between 2002 and 2007. After institutional review board approval, charts were reviewed to determine percent TBSA burned, injury severity score (ISS), propranolol and amounts given, total number of surgeries at the military burn center, and the anesthetic regimen used, including amounts given. Patients were sorted based on whether or not they received propranolol. Thirty-one patients received propranolol and 195 did not. To achieve groups with similar demographics (~37% TBSA and ~27 ISS), all patients with burns 20% or greater (n = 34), who did not receive propranolol, were used for analysis (Figure 1).

The PCL-M is a self-report screening tool for PTSD that is authorized for use by the U.S. military. It consists of 17 questions rated on a scale of 1 to 5 with a possible total score of 17 to 85. A score of 44 or higher yields a diagnostic efficiency of 0.900[23] so for this study a score of 44 or greater was considered diagnostic for PTSD. The questions are designed to capture one of three distinct clusters of symptoms: re-experiencing, avoidance/numbing, or hyperarousal. The complete diagnostic criteria for PTSD are described in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (1994).[7] The PCL-M was divided into subgroups. Questions 1, 2, 4, and 13 were subgrouped as to re-experiencing and nightmares.

To identify anesthetic agents used by the subjects in the study, medical records were reviewed. Intraoperative ketamine usage in milligrams was calculated by adding the amount of ketamine received in the operating room. Intraoperative morphine equivalent units from the operative procedures were calculated by converting opioids (morphine, hydromorphone, fentanyl, sufenta, and methadone) into IV morphine equivalents via the opioid calculator at www.medcalc.com/narcotics.html.

RESULTS

This study examined the prevalence of PTSD in burn patients who received propranolol compared with those

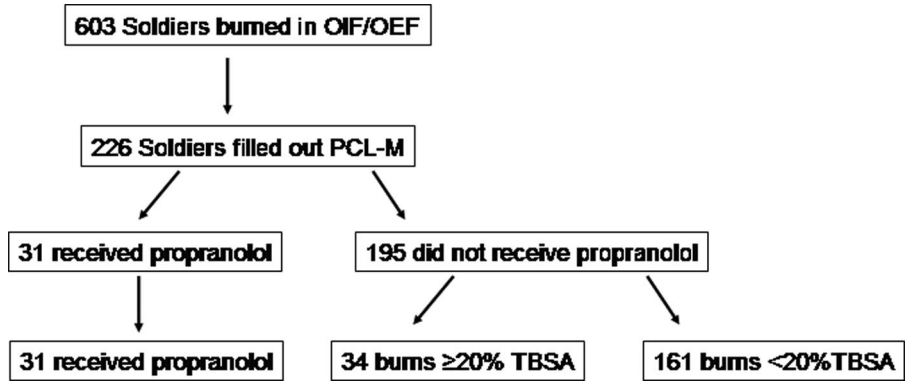

Figure 1. Schematic representation of the groups of propranolol and no propranolol. United States Army Institute of Surgical Research received 603 patients that were burned during Operation Iraqi Freedom and Operation Enduring Freedom. Of those, 226 filled out the PCL-M. Of those 226, 195 did not receive propranolol in the standard course of their treatment and 31 did. Of the 195 that did not receive propranolol, 34 had burns larger than 20% TBSA. *PCL-M*, Posttraumatic stress disorder Checklist-Military; *OIF/OEF*, Operation Iraqi Freedom/Operation Enduring Freedom.

who did not receive propranolol. Of the soldiers injured in OIF/OEF, the military burn center received 603 casualties over the 5-year period, of which 226 completed the PCL-M. Of those, 31 soldiers received propranolol and 195 did not. Of those receiving propranolol the prevalence of PTSD was 32.3% (10 of 31) vs 26.6% in those not receiving propranolol (52 of 195) (Table 1). However, the demographics of these groups suggested that propranolol patients were more severely injured with approximately four times larger TBSA and approximately three times higher ISS scores (Table 1). Propranolol patients were also more likely to undergo more operations and receive more intraoperative morphine equivalents (Table 1).

There was some concern that PTSD development was related to burn size or injury severity despite several studies that have suggested that burn size is not related to PTSD development.[9–12,24] To achieve a more equal TBSA, all patients with burns greater than 20% TBSA who did not receive propranolol were selected (34 patients) to be used as a control group (Figure 1). The prevalence of PTSD in each group was similar (propranolol 10 of 31 [32.3%] and no propranolol 9 of 34 [26.5%]) (Table 2). There was no statistical difference in these prevalence rates using the χ^2 test ($P = .785$). Patients receiving propranolol had the same TBSA, underwent the same number of operations, received the same amount of ketamine and morphine equivalent units during operative procedures as nonpropranolol receiving patients, but propranolol patients had higher ISS scores ($P < .05$) as determined by the Mann-Whitney test. The demographics of the propranolol group and the no propranolol group are shown in Table 3.

Spearmans test was used to determine correlation between propranolol, PTSD, and other factors. PTSD and propranolol have a correlative r value of .064 (Table 4), which indicates no association between these two variables. However, propranolol does correlate with ISS, TBSA, and other markers of injury severity (Table 4).

Logistical regression analysis with propranolol to predict PTSD yielded a value of 0.0008028, which was not significant ($P = .366$). Receiver operated

Table 1. Prevalence of PTSD and demographics in propranolol and no propranolol group

	No Propranolol	Propranolol
Patients	195	31
Scoring positive for PTSD	52	10
Prevalence of PTSD	26.6%	32.3%
TBSA	10 ± 10.9*	38 ± 19*
ISS	8 ± 8.4*	27 ± 11*
Operations	1 ± 1.5*	4 ± 3.4*
Morphine equivalent units received in operating room	76 ± 175*	380 ± 435*
Age	25.2 ± 5.9	26.6 ± 5.9

* $P < .05$. Propranolol patients were more injured that no propranolol patient but the prevalence of PTSD is not significantly different.
PTSD, posttraumatic stress disorder; *ISS*, injury severity score.

Table 2. Prevalence of PTSD in propranolol group and nonpropranolol group ($P = .745$)

	Propranolol	No propranolol
Patients	31	34
Scoring positive for PTSD	10	9
Prevalence of PTSD, %	26.5	32.3

PTSD, posttraumatic stress disorder.

Table 3. Demographics of propranolol and nonpropranolol group

	Propranolol (N = 31)	No Propranolol (N = 34)
TBSA	31.8 ± 13.13	37.5 ± 19.58
ISS	22.38 ± 9.54*	27.29 ± 11.51*
Operations	2.56 ± 2.44	3.68 ± 3.61
Intraoperative ketamine	537.9 ± 569.7	261.62 ± 375.9
Intraoperative morphine equivalent units	389.7 ± 466.6	297.5 ± 330.5
Age	26 ± 5.1	25.8 ± 6.1

* $P < .05$.
ISS, injury severity score.

curve analysis with propranolol to predict PTSD gave an area under the curve of 0.56 suggesting that propranolol usage is not a good predictor of PTSD.

In other studies, propranolol has been shown to alter memory and memory reconsolidation.[17,19] To determine whether propranolol was associated with decreased intensity of memory of the traumatic event in burned soldiers, we used the PCL-M to assess intensity. The PCL-M is a self-reported PTSD screening tool that consists of 17 questions rated on a scale of 1 to 5, with a possible score ranging form 17 to 85. A score of 44 or higher is considered a positive screen for PTSD.[23] The PCL assesses three areas: avoidance/emotional numbing, re-experiencing, and hyperarousal.

Four questions in the PCL-M address the issue of nightmares and sleep disturbances, questions 1, 2, 4, and 13. Question 1 addresses repeated, disturbing memories, thoughts, or images of a stressful military experience. These symptoms could occur while the patient is awake or asleep when re-experiencing the memory. Question 2 addresses repeated, disturbing dreams of a stressful military experience. Disturbing dreams could occur while the patient is asleep and re-experiencing the traumatic event. Question 4 addresses feeling very upset when something reminded you of a stressful military experience. Feeling upset could occur either during sleep or wake periods. Question 13 addresses trouble falling or staying asleep. Sleep could be disturbed because of intrusive memories or nightmares.

Table 4. Correlation between propranolol and PTSD development. There is no significant correlation between PTSD and propranolol administration but there is a significant correlation between propranolol and injury severity (ISS, TBSA, total amount of ketamine, morphine equivalent units, and number of operations)

	Propranolol	
	R	Significance
PTSD	.102	0.418
TBSA	.332*	0.007
ISS	.372*	0.002
Operations	.229	0.066
Intraoperative ketamine	.327*	0.008
Intraoperative morphine equivalent units	.187	0.137

* $P < .05$.
PTSD, posttraumatic stress disorder; *ISS*, injury severity score.

Patients receiving propranolol had no significant differences in overall scores on the PCL-M from patients not receiving propranolol. Moreover, propranolol usage was not related to the scores of questions 1, 2, 4, and 13 even though they deal with re-experiencing the traumatic event (Table 5). These data suggest that administration of propranolol does not alter the prevalence of PTSD, and they have no effect on the severity of disturbing dreams, which might prevent better sleep (question 2).

When the data were sorted by PTSD development, physical characteristics of injury such as TBSA ($P = .436$), ISS ($P = .777$), number of operations ($P = .848$), amount of morphine equivalent units during operative procedures ($P = .54$), amount of ketamine during operative procedures ($P = .497$), propranolol usage ($P = 0.611$), and amount of propranolol ($P = .413$) were not significantly different in patients that developed PTSD compared with those that did not (Mann-Whitney *U*). Nor was there a correlative association between PTSD and physical characteristics of the burns (data not shown).

Limitations

There are several limitations to this study including the fact that this was a retrospective study with all the inherent limitations. The use of propranolol with burned patients is at the discretion of the physician, thus not every patient in the study received propranolol. For this study, serum concentrations of propranolol were not considered, and the timing of dosage along the recovery path was not able to be determined from patient records. Only a small number of patients who received propranolol completed the PCL-M. Controls were selected from patients who completed the PCL-M, had burns greater than 20% TBSA, and did not receive propranolol in their treatment course. Study groups were matched for demographics. Individual patients were not matched for TBSA and ISS because of the small sample size. The propranolol group had larger ISS scores than the no propranolol group, which raises the concern that injury severity is linked to PTSD development, thus, the

Table 5. Effect of propranolol on nightmares and sleep disturbances. The average score for PCL-M questions 1, 2, 4, and 13

Question	Propranolol	No propranolol
1. Repeated, disturbing memories, through or images of a stressful military experience?	2.47 ± 1.41	2.66 ± 1.41
2. Repeated, disturbing dreams of a stressful military experience?	2.2 ± 1.49	2.34 ± 1.41
3. Suddenly acting or feeling as if a stressful military experience were happening again (as if you were reliving it)?	1.93 ± 1.33	1.94 ± 1.24
4. Feeling very upset when something reminded you of a stressful military experience?	2.73 ± 1.31	2.38 ± 1.18
5. Having physical reactions (heart pounding, trouble breathing, or sweating) when something reminded you of a stressful military experience?	2.3 ± 1.47	2.09 ± 1.0
6. Avoid thinking about or talking about a stressful military experience or avoid having feelings related to it?	2.2 ± 1.4	2.28 ± 1.22
7. Avoid activities or situations because they remind you of a stressful military experience?	1.83 ± 1.23	2.06 ± 1.29
8. Trouble remembering important parts of a stressful military experience?	1.80 ± 1.32	1.84 ± 1.11
9. Loss of interest in things that you used to enjoy?	2.00 ± 1.4	1.68 ± 1.05
10. Feeling distant or cut off from other people?	1.73 ± 1.11	1.84 ± 1.11
11. Feeling emotionally numb or being unable to have loving feelings for those close to you?	1.43 ± 0.86	1.66 ± 1.15
12. Feeling as if your future will somehow be cut short?	1.87 ± 1.57	2.03 ± 1.38
13. Trouble falling or staying asleep?	2.97 ± 1.56	2.78 ± 1.64
14. Feeling irritable or having angry outbursts?	2.50 ± 1.36	2.41 ± 1.16
15. Having difficulty concentrating?	2.23 ± 1.33	1.97 ± 1.23
16. Being "super alert" or watchful on guard?	2.20 ± 1.37	2.41 ± 1.39
17. Feeling jumpy or easily startled?	2.43 ± 1.36	2.28 ± 1.22

* $P < .05$.
PCL-M, Posttraumatic Stress Disorder Checklist-Military.

more severe injury may be masking the effect of propranolol on PTSD formation. This study makes the assumption that PTSD is based on the traumatic event that resulted in the patient's burn. It neither address treatment issues, such as pain during treatment influence the development of PTSD nor their influence on the development of PTSD.

DISCUSSION

A 2007 report from the Institute of Medicine recommended that the most successful PTSD treatment is prolonged exposure therapy, which desensitizes the patient to the traumatic event over a lengthy period of time.[25] The data presented in our study echo the Institute of Medicine findings that propranolol administration is not an effective treatment to prevent PTSD: however, propranolol's use in minimizing the hypermetabolic response remains clinically important.

Our data suggest that propranolol does not decrease PTSD development in burned soldiers. The prevalence of PTSD in propranolol receiving patients is not statistically different than those not receiving propranolol. Overall, the patients receiving propranolol had significantly larger burns, higher ISS, receive more ketamine, and underwent more operations. However, when the groups were matched for TBSA burned, the demographics became similar and the prevalence of PTSD in these cohorts was statistically comparable.

Although our propranolol cohort did not demonstrate a decreased incidence of PTSD, the effect or use of propranolol administration on PTSD prophylaxis remains unclear. This retrospective study examined the administration of propranolol coincident with PTSD rates. It did not take into an account psychological counseling that soldiers receive or when the psychological counseling occurred in relation to propranolol administration. Because memory reactivation is required for propranolol to disrupt the memory,[14] the timing of propranolol and the psychological counseling resulting in memory reactivation needs to be investigated further.

There is also the concern that patients with large burns (>20% TBSA) may be too hypermetabolic to be affected by the administration of propranolol. Most of the human research done with propranolol in burn has been in a pediatric population.[26] In this study, patients were administered a dose of propranolol, but absorption and systemic levels were not measured. Unlike treatment for heart failure and coronary artery disease, a target rate for burn patients has not been determined. For analysis, patients were clas-

sified into a yes or no category for receiving propranolol and propranolol concentrations were not assessed.

Our data suggest that burn size is not related to PTSD development in civilian or military patients.[9–12,24] One possible explanation is that the trauma of the burn regardless of the severity is enough to cause PTSD. Another possible explanation is that untreated pain may intensify PTSD development. In this single center study, propranolol is more likely to be given to sicker patients: an obvious selection bias. Although a higher PTSD incidence would be expected with more critically wounded soldiers, this was not demonstrated in our cohort. This suggests there may be a yet indeterminate benefit in decreased incidences of PTSD after propranolol administration. A larger study with longer follow-up would be helpful in elucidating possible relationships. Further studies are needed to determine the relationship between anesthetic drugs and PTSD development as well as studies that coordinate the effects of multi-modal treatment modalities on long-term outcomes of PTSD.

CONCLUSION

These data suggest that propranolol treatment did not statistically alter the prevalence of PTSD in this cohort of burned soldiers. In our population of 226 patients, propranolol administration was associated with increased injury severity including higher ISS, larger TBSA burned, more operations, greater interoperative opioid requirements: however, when the groups were matched for TBSA burned, there were no differences between these physical characteristics. Propranolol usage was not a good predictor of PTSD development, and propranolol usage did not affect the incidence of nightmares as evidenced by scoring of question 2 on the PCL-M and does not increase the intensity of upset after reminder of a traumatic event (questions 1, 2, 4, and 13 on the PCL-M).

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