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Review

Prevention of posttraumatic stress disorder with propranolol: A meta-analytic review

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ABSTRACT

Objective: PTSD is associated with significant morbidity and its prevention could reduce a significant burden of individual and societal suffering. The aim of this study is to conduct a systematic review of the literature on the prevention of PTSD by using propranolol following exposure to a traumatic event.
Methods: Authors searched all studies published in the MEDLINE database up to November 2014 and reviewed textbooks and reference lists. Authors of relevant articles were contacted. Clinical trials and observational studies were included if they investigated the effect of propranolol in the acute post-trauma phase to prevent PTSD symptoms for subjects 18 years of age or older. PTSD was diagnosed according to DSM or widely accepted and validated diagnostic tools. A random-effects model was used to perform meta-analysis.
Results: Five studies were included in the review for meta-analysis. Heterogeneity was not significant ($\tau^2 = 0.0$, S.E = 0.247; Cochran's $Q_{(4)} = 1.870$, $p = 0.760$; $I^2 = 0\%$). Relative risk point estimate to the effect of propranolol to prevent PTSD was 0.92 (95% CI: 0.55–1.55). Asymmetry was not significant under the Egger test ($z = -1.34$; $p = 0.180$).
Conclusions: The findings suggest that propranolol treatment after the traumatic event did not alter the incidence of PTSD, although physiological responses are generally attenuated. The studies included small sample sizes, which can preclude the detection of significant results. Authors believe future studies should achieve larger sample sizes and longer follow-up periods.

Introduction

Many people experience a potentially traumatic event (TE) on a daily basis and most of the adult population experiences at least one TE in the course of life [1,2]. TE is defined as exposure to an actual risk or threat of death, serious injury, or sexual violence and may be experienced directly, by witnessing another person experiencing trauma or by learning about trauma experienced by a family member or close associate [3]. After exposure to a TE, many people may have event-related symptoms, such as intrusive symptoms, having negative alterations in cognition and mood, physiological hyperarousal and avoidant behavior. If these symptoms occur for more than one month and are associated with clinically significant distress or impairment in social and occupational aspects or other important area of functioning, the criteria for posttraumatic stress disorder (PTSD) are met [3].

Results from the World Health Organization (WHO) World Mental Health (WMH) Survey Initiative show a prevalence of 4% across the subjects exposed to TE [4]. This disease is frequently associated with significant morbidity, poor quality of life, and lower educational and occupational success [5–7]. In addition, it is also associated with greater levels of physical disability [8] and increased use of medical services [9,10]. Therefore, prevention of PTSD can potentially reduce a significant burden of individual and societal suffering. Since diagnosis of PTSD requires the presence of a TE, there is an effort to identify treatments or interventions that prevent PTSD after trauma [11,12].

Studies have provided compelling evidence that the presence of a prolonged adrenergic activation during a life-threatening event contributes to overconsolidation of memory for the trauma and thereby supports the development of the intrusive symptoms found in PTSD [13–15]. Some researchers have suggested the possibility of using a lipophilic beta-adrenergic receptor antagonist, especially propranolol, to prevent PTSD [16–19]. The aim of using propranolol would be to prevent the embedding of pathological unconscious emotional memories of fearful events in the amygdala [16]. Based on this reasoning, the administration of propranolol would be cost-effective for the prevention of future individual, social and economic costs. On

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the other hand, in spite of the evidence referenced above, if the use of beta-adrenergic receptor antagonist (Beta blocker) prevents PTSD, what explains the high incidence of PTSD resulting from a heart attack event (approximately 14.7% [20]) is not clear. Oral Beta blocker use ought to begin as soon as the subject shows the first symptoms, with few exceptions, and be continued during and after hospitalization [21]. If the use of this medication is effective in preventing PTSD, this incidence value should be lower. The fact is that other studies have shown that, even though propranolol impaired the memory consolidation process, it was ineffective to prevent the onset of PTSD [22–24], indicating that the pathophysiology of PTSD involves numerous other physiological systems and interactions [22].

Therefore, the main purpose of this study was to conduct a systematic review of the literature on the attempted pharmacological prevention of PTSD by using propranolol after a traumatic event, in order to investigate the potential effects of the use of propranolol in the post-trauma acute phase. Meta-analysis was performed using data from studies which matched the given criteria. The main hypothesis was that propranolol treatment after the traumatic event would not significantly alter the incidence of PTSD after adjustment for methodological differences across studies.

Methods

Review was performed following Cochrane protocol and reported using PRISMA statement guidelines [25].

Eligibility criteria

Study designs included observational studies and clinical trials investigating the effect of propranolol in the acute post-trauma phase to prevent PTSD symptoms. Reference lists of articles identified through database searches and bibliographies of systematic or non-systematic review articles were examined to identify further relevant studies. Subjects aged 18 years or older who had experienced potentially traumatic experiences were included and intervention was compared to placebo or no intervention. Studies published up to November 2014 in Spanish and English were selected. The PTSD diagnosis was conducted by specialists using DSM criteria or widely accepted and validated diagnostic tools.

Information sources and study selection

Research was conducted between April and November 2014 using PubMED tool (granting access to the MEDLINE database and additional references from the National Library of Medicine). All material published up to November 2014 was included. The following string terms were used: ("Propranolol"[Mesh]) and "Stress Disorders, Post-Traumatic"[Mesh]; Propranolol and PTSD; (("Stress Disorders, Post-Traumatic/etiology"[Mesh] or "Stress Disorders, Post-Traumatic/physiopathology"[Mesh] or "Stress Disorders, Post-Traumatic/prevention and control"[Mesh])) and "Propranolol"[Mesh]. Clinical trials that were canceled or currently in progress were searched on the ClinicalTrials.gov website using keywords "Propranolol and PTSD".

Studies were identified and selected independently by two reviewers according to inclusion and exclusion criteria. A third independent reviewer was available to arbitrate in case of disagreement over a selection.

Data extraction

Data was extracted using a form designed by both independent primary reviewers and approved by the third reviewer, containing: study design (setting); sample characteristics; intervention description (trauma-drug interval, dosage and duration); control (comparison treatment); and outcome assessed.

Methods and biases were evaluated independently by the reviewers. Only studies selected by both were included.

Summary measure

Relative risk was chosen as summary measure instead of odds ratio, given its simple interpretation for clinicians and that all studies provided raw data of their outcome proportions between intervention patients and controls.

Methods of analysis

Analysis was conducted using a random effects model, since study designs were not totally equal. However, fixed effects model results are also provided in the electronic supplementary material. Heterogeneity (τ^2) was estimated by the restricted maximum-likelihood-estimator method (RMLE) and tested using Cochran's Q-test. RMLE is considered to be robust and unbiased for random effects models [26]. Risks for publication bias were assessed by funnel plot analysis. Asymmetry was tested using the random effects version of the Egger's test [27]. Analysis was performed using the metafor [28] package in the R environment and programming language [29].

Results

Initial searches returned 187 published texts. After filtering for duplicate results and papers with an abstract not related to the subject, 29 studies were screened for primary analysis. A total of 24 studies were subsequently excluded for not meeting inclusion criteria, resulting in five studies qualifying for meta-analysis in the review. Fig. 1 displays the process flow regarding study selection.

Three of the five studies were randomized controlled trials, one was an open study, and one was an observational retrospective study. Each of these studies involved patients presenting to trauma centers for physical injuries: four studies included civilian subjects and one study enrolled military soldiers. Data extracted from the five selected studies is summarized in Table 1.

In the first study, Pitman and colleagues [16] recruited 41 emergency department (ED) patients who had experienced a traumatic event and had a heart rate (HR) of 80 beats per minute or higher at the time of ED presentation. They were randomized to receive 40 mg of propranolol or placebo four-times daily for 10 days (followed by a 9-day taper period), starting no longer than 6 h after the TE. Eleven propranolol patients and twenty placebo patients completed the study. The investigators found a statistically non-significant trend for the propranolol patients to have lower average Clinician-Administered PTSD Scale (CAPS) scores than the placebo patients. During script-driven imagery performed at 3 months, none of the 8 propranolol patients and 8 of 14 placebo patients showed a significantly elevated physiologic response.

Vaiva et al. [17] carried out a non-randomized trial with 19 ED patients who had experienced a traumatic event accompanied by physiological arousal (tachycardia of at least 90 beats/min). Eleven patients agreed to take 40 mg of propranolol 3 times daily for 7 days (followed by a 8–12-day taper period), and the first dose was no longer than 20 h after the TE. Eight patients who refused to take the propranolol, but agreed to participate in the study, made up the control group. Two months after the traumatic event, the patients who refused propranolol were significantly more likely to suffer PTSD and to experience PTSD symptoms than those who took the drug.

In a randomized double-blind placebo-controlled trial conducted by Stein et al. [23], injury patients admitted to a surgical trauma center were assessed at hospital intake and followed prospectively for 8 months. 48 enrolled subjects (5062 were initially screened) were randomized to receive propranolol (n = 17), gabapentin (n = 14) or a placebo (n = 17). Propranolol was started within 48 h of injury and 40 mg was administered 3 times daily for 8 days (followed by a 4-day taper period). Patient assessments were conducted by telephone at 1-, 4- and 8-months post-injury. Although the Posttraumatic Stress Disorder Checklist—Civilian Version (PCL-c) scores declined significantly over time, none of the drug cohorts in the study differed significantly from one another over time in the reduction of PTSD symptoms.

In a retrospective study [30], burned soldiers who received propranolol were compared with those who did not receive propranolol. PTSD incidence was not significantly different between the two groups, and this result did not change after adjusting for injury severity, such as total body surface area score, number of operations, and anesthetic agents used by the subjects at the military burn center. However, propranolol dose and timing were not considered in this study, and, furthermore, propranolol was more likely to be given to patients with more severe cases.

Lastly, Hoge et al. [24] randomized 41 ED patients (2014 were initially screened), who had experienced a traumatic event, to receive within 12 h an initial dose of either 40 mg short-action propranolol or placebo. One hour after this first dose, an additional dose of 60 mg long-acting propranolol or placebo was given. Participants continued taking long-acting propranolol (or placebo) at home over a 19-day course, starting with