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Research report

Intermittent treatment with haloperidol or quetiapine does not disrupt motor and cognitive recovery after experimental brain trauma

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HIGHLIGHTS

- Intermittent haloperidol does not negatively impact functional outcome after experimental brain trauma.
- Intermittent quetiapine does not negatively impact functional outcome after experimental brain trauma.
- Daily administration of haloperidol negatively impacts functional outcome after experimental brain trauma.
- Daily administration of quetiapine does not negatively impact functional outcome after experimental brain trauma.
- These findings suggest that quetiapine may be a safer alternative to haloperidol for managing TBI-induced agitation.

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ABSTRACT

Traumatic brain injury (TBI)-induced agitation and aggression pose major obstacles to clinicians in the acute hospital and rehabilitation settings. Thus, management of these symptoms is crucial. Antipsychotic drugs (APDs) are a common treatment approach for alleviating these symptoms. However, previous preclinical TBI studies have indicated that daily and chronic administration of these drugs (e.g., haloperidol; HAL) can exacerbate cognitive and motor deficits. Quetiapine (QUE) is an atypical APD that differs from many typical APDs, such as HAL, in its relatively rapid dissociation from the D_2 receptor. The goal of this study was to test the hypotheses that intermittent HAL and QUE would not hinder recovery of cognitive and motor function following TBI and that daily QUE would also not impair functional recovery, which would be in contrast to HAL. Seventy anesthetized male rats received either a controlled cortical impact or sham injury and were then randomly assigned to TBI and sham groups receiving HAL (0.5 mg/kg) or QUE (10 mg/kg) intraperitoneally once per day or once every other day and compared to each other and vehicle (VEH) controls. Motor function was assessed by beam balance/walk tests on post-operative days 1–5 and cognitive function was evaluated with a Morris water maze task on days 14–19. No differences were revealed among the sham groups in any task, and hence the data were pooled. No overall differences were detected among the TBI groups, regardless of treatment or administration paradigm [$p > 0.05$], but all were impaired vs. SHAM controls [$p < 0.05$]. The SHAM controls also performed significantly better in the cognitive test vs. all TBI groups [$p < 0.05$]. Moreover, the TBI + continuous HAL group performed worse than the TBI + continuous VEH, TBI + continuous QUE, and TBI + intermittent QUE groups [$p < 0.05$], which did not differ from one another. Overall, the data suggest that QUE does not exacerbate TBI-induced cognitive and motor deficits, which supports the hypothesis. QUE may prove useful as an alternative APD treatment for management of agitation and aggression after clinical TBI. HAL may also be safe, but only if used sparingly.

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1. Introduction

Traumatic brain injury (TBI) is a highly prevalent clinical issue affecting an estimated 1.7 million Americans annually [1–3]. TBI contributes to numerous pathophysiological conditions and adverse neuropsychiatric disturbances [4]. In many cases, extensive rehabilitative care is required. However, disinhibited behavior, including severe agitation and aggression, is common after moderate to severe TBI [5–10]. Such symptoms pose a risk to the health and safety of patients and caregivers, as well as significantly impede rehabilitation [6–11]. Management of agitation and aggression is therefore crucial, and typical and atypical antipsychotic drugs (APDs) are frequently employed to alleviate such issues. Extended use of these APDs, however, presents a number of possible problems, as evidence suggests they exacerbate motor and cognitive deficits and slow the rate of recovery [12–15].

Haloperidol (HAL) is a popular first-generation APD frequently used to manage post-TBI agitation. Preclinical studies using fluid percussion and cortical impact TBI models have demonstrated that chronic administration of HAL impairs motor and cognitive recovery [12–15]. The impairment persists whether the drug is administered before or after behavioral testing, suggesting the deleterious effects are not due simply to behavioral sedation, and endure for up to three months after drug discontinuation [12,15]. Like many of the APDs commonly used to alleviate post-TBI agitation, HAL exerts its effects by acting as a high-affinity D_2 receptor antagonist. Quetiapine (QUE), on the other hand, is a second-generation APD with considerably lower affinity for D_2 receptors [16,17]. Prior research has demonstrated that neither single nor repeated administrations of the atypical APDs clozapine and olanzapine, both of which have D_2 receptor affinities comparable to that of QUE, has a negative impact on cognitive and motor performance after TBI [14,18]. The rationale for evaluating QUE is that it is one of the most widely accepted treatments currently for managing agitation and aggression in the clinic.

When considering the use of antipsychotic medications to manage symptoms that may disrupt rehabilitation, treatment strategies may vary depending on short-term versus long-term needs and goals for patient care. Some evidence suggests that a single administration of HAL after injury does not disrupt cognitive and motor recovery except at high doses, while daily administration for five days exacerbates cognitive and neurobehavioral deficits [12,13,15,19]. A realistic clinical strategy may rely on these medications prior to rehabilitation sessions and thus may not entail daily administration. However, the majority of research on APDs following TBI has focused on a daily drug regimen, the effects of which may differ from a periodic and potentially more clinically relevant administration schedule.

Hence, the present study aimed to evaluate the effects of continuous or intermittent treatment with QUE or HAL on short-term functional recovery after a controlled cortical impact (CCI) injury in adult male rats. The intermittent schedule was intended to simulate a clinically relevant course of drug administration where patients may not necessitate APD treatment every day. Motor function, spatial learning, and memory were assessed during this period to compare behavioral outcomes and how they may be affected by the APDs and the treatment schedule.

2. Materials and methods

2.1. Subjects and pre-surgical procedures

Seventy adult male rats (Harlan Sprague-Dawley, Indianapolis, IN) were paired housed in ventilated polycarbonate rat cages and maintained in a temperature ($21 \pm 1\,^{\circ}C$) and light (on 0700–1900 h) controlled environment with food and water available *ad libitum*. During their week of acclimatization, the rats were pre-trained on the beam-walk task and then randomly assigned to one of the following group conditions: TBI + continuous vehicle (1.0 mL/kg; n = 10), TBI + continuous haloperidol (0.5 mg/kg; n = 10), TBI + continuous quetiapine (10 mg/kg; n = 10), TBI + intermittent haloperidol (0.5 mg/kg; n = 10), TBI + intermittent quetiapine (10 mg/kg; n = 10), and Sham controls for each condition (n = 20). All experimental procedures were approved by the Institutional Animal Care and Use Committee at the University of Pittsburgh. Every attempt was made to limit the number of rats used and to minimize suffering.

2.1.1. Surgery

Controlled cortical impact (CCI) was produced as previously described [20–23]. Briefly, surgical anesthesia was induced and maintained with 4% and 2% concentrations of isoflurane, respectively, in 2:1 N_2O:O_2. After endotracheal intubation the rats (275–300 g) were secured in a stereotaxic frame and ventilated mechanically. Core temperature was maintained at $37 \pm 0.5\,^{\circ}C$ with a heating pad. Utilizing aseptic procedures a midline scalp incision was made, the skin and fascia were reflected to expose the skull, and a craniectomy (6-mm in diameter) was made in the right hemisphere with a hand held trephine. The bone flap was removed and the craniectomy was enlarged further to accommodate the impact tip (6 mm, flat), which was centered and lowered through the craniectomy until it touched the dura mater. Once confirmed that the impact tip was touching the dura, the rod was retracted and the impact tip was advanced 2.8 mm farther to produce a brain injury of moderate severity (2.8 mm tissue deformation at 4 m/s). Anesthesia was discontinued immediately after the impact and the incision was promptly sutured. The rats were subsequently extubated and assessed for acute neurological outcome. Sham rats underwent all surgical procedures, except the impact.

2.1.2. Acute neurological evaluation

Hind limb reflexive ability was assessed immediately following the cessation of anesthesia by gently squeezing the rats' paw every 5 s and recording the time to elicit a withdrawal response. Return of the righting reflex was determined by the time required to turn from the supine to prone position on three consecutive trials.

2.1.3. Drug administration

HAL (Sigma) and QUE (Tocris) were prepared daily by dissolving in 1:1 dimethyl sulfoxide (DMSO)/saline, which also served as the vehicle (VEH). The dose of HAL was chosen because it has been reported to be comparable to that used clinically to control psychosis [24] and has been used in several brain injury studies investigating functional outcome [12,13,15,19,25]. The dose of QUE was chosen based on the preclinical literature [26]. Treatments began 24 h after CCI or sham surgery and were provided intraperitoneally once daily or once every other day (i.e., intermittently) for 19 days. Both HAL and QUE were administered *after* the daily behavioral assessments to circumvent sedative effects, which would confound the results.

2.1.4. Motor performance: beam-balance and beam-walk

Motor function was assessed using the well-established beam-balance and beam-walk tasks [20–23]. Briefly, performance on the beam-balance is assessed by recording the time that the rats can maintain their balance on an elevated narrow wooden beam (90 cm above floor level, 1.5 cm wide, and 34 cm in length). The beam-walk task, modified from that originally devised by Feeney and colleagues [27], and used extensively in our laboratory [20–23], consists of assessing rats using a negative-reinforcement paradigm to escape a bright light, shining at the start point, and white noise

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