



Pharmacological Management of Agitation and Aggression in Emergency Department

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ABSTRACT

Agitation and violent commonly occur in Emergency Department (ED). This is very important to manage agitated patients as soon as possible to prevent them from harming themselves or other patients and health care providers. Early management allows Clinicians to perform physical examination and appropriate treatment. Current studies recommended antipsychotics, Benzodiazepines and antidepressants. The purpose of this review is to evaluate pharmacological treatment for the management of agitation and aggression in ED. Our study is a comprehensive literature search to define recent drugs that are currently using for the treatment of agitation and aggression in ED. This review recommended that pharmacological treatments, such as antipsychotics, ketamine, promethazine, on-steroidal anti-inflammatory drugs, analgesics, narcotics may create more treatment option for the management of agitation and aggression in ED that requires more studies in order to show their risks and benefits.

Key words: Temporomandibular joint, Cone-beam computed tomography, Three-dimensional image, Software

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ABBREVIATIONS

SGA: Second Generation Antipsychotic; FGAS: First Generation Antipsychotic; ECT: Electroconvulsive Therapy; APA: American Psychiatric Association; PANSS: Positive and Negative Syndrome Scale; PANSS-EC: PANSS Excited Components; PPC: Peak Plasma Concentration

INTRODUCTION

Emergency physicians frequently face the agitated, aggressive and violent patients that may be due to psychosis, acute intoxication or withdrawal, delirium state, head trauma, CNS infection or brain dysfunction. This is an important issue to manage agitated patients as soon as possible to prevent them from harming themselves or other patients and health care providers. Early management allows clinicians to perform physical

examination, diagnostic testing and initiate appropriate treatment.

Caregivers must control these patients with chemical restrain by the administration of sedative hypnotic, or antipsychotic or dissociative medications.

In 1992, most medication prescribed were haloperidol, diazepam and droperidol for rapid management of aggressive patients in emergency department (ED). Various drugs were used in emergency department for management of aggressive patients, for example in 1993 chlorpromazine was the common choice in the UK. In 1999 combination of haloperidol-lorazepam was used at ED for calming the aggressive patients. In 2002 preferred medical management for agitated patients were combination of haloperidol and promethazine [1].

Management of agitation in Alzheimer's disease

Current researches recommended atypical antipsychotic for the control of agitation in Alzheimer's disease. These treatments are effective in management of agitation but can increase serious adverse effects including cardiovascular events and mortality, so risperidone

and olanzapine should not be administered in Alzheimer's disease. Sertraline and citalopram can improve the symptoms of aggression and agitation in dementia. Administration of analgesics such as acetaminophen, opioid (morphine, buprenorphine) may control the agitation and aggression in dementia patients on the mechanism of pain management [2].

Ketamine

Ketamine is a dissociative drug that causes analgesia and amnesia. It is used in ED for the procedural sedation and as an induction agent for intubation. The American College of Emergency Physicians, accepted ketamine as a first-acting agent in agitated patients in ED with rapid onset, under 4 minutes. It has low risk of side effects. The rapid onset of ketamine is comparable to haloperidol with peak plasma time of 10-20 minutes.

Ketamine can cause tachycardia and HTN in nonagitated patients, but this occurs rarely significantly. Additional management medication was antipsychotics, benzodiazepines, or ketamine which added if agitation remains after 3 h of the first dose of ketamine [3].

Patients with alcohol/substance toxicity require higher dose of additional medication for management of agitation. Ketamine can be administered in both IM and IV access with rapid onset of action. Ketamine does not treat the etiology of the agitation and aggression. Because of dissociative state of these patients, they can't cooperate with their own care. Ketamine should not be administered in the setting of pre hospital, because it may cause decrease in oxygen saturation. Reduction of O₂ saturation is not significant hence causing hypoxia [3].

Antipsychotic

Use of SGAs is preferred to FGAs, because these drugs are associated with lower risk of extrapyramidal symptoms and other adverse effects such as weight gain, elevated lipid and prolactin levels, and further cardiovascular morbidity and mortality [4].

Increase doses of antipsychotics reduce aggression and agitation more significantly. Antipsychotics have more antiaggressive effects, if the patients experience improvement in underlying disease, for example they feel disappearance of an underlying manic phase [5].

A randomized double-blind study was carried out by Lavania *et al*. In this study acute psychotic patients were randomly treated in two groups. In one group patients with psychosis treated with intramuscular haloperidol (10-20 mg/d) and the other group treated with Levosulpiride injection (25-50 mg/d) [6].

Brief psychiatric rating scale (BPRS) has been one of the most frequently used tools to measure psychiatric symptoms including depression, anxiety, hallucinations and unusual behavior [6]. Overt Agitation Severity Scale

(OASS) is a new instrument that is used to identify the severity of agitated behavior. The Modified Overt Aggression Scale (MOAS) is one of the instruments that has been used to measure four types of aggressive behavior, each part consists of some questions including: verbal aggression, aggression against property, autoaggression, physical aggression. This scoring has shown good reliability and validity in multiple different studies [6].

For BPRS and (OAS-m) repeated-measures ANOVA showed significant effect of time (0.001>P) and greater reduction in scores in patients received haloperidol (Im) [6].

METHODOLOGY

In this study we demonstrated improvement in psychotic symptoms, agitation, and aggression with both Levosulpiride and haloperidol injection and higher improvement with haloperidol.

The improvement was observed by giving Levosulpiride and haloperidol injection in the initial 4 days and higher decrease in symptoms were noticed with haloperidol.

In one of the randomized controlled trials (RCT) study, droperidol was compared with placebo to induce hypnotic effects in aggressive patients by 30 minutes showed significant difference between them. (1 RCT, N=227, RR: 1/18, high-quality evidence). There was significant decrease in requirement of other medication after 60 minutes for the group that received droperidol (high-quality evidence) [1].

In another RCT study, droperidol was compared to haloperidol to induce hypnotic effects in aggressive patients by 30 minutes, which showed significant difference between them (high-quality evidence). In another RCT, droperidol was compared with midazolam to induce hypnotic effects in aggressive patients by 30 minutes, which showed droperidol had less acutely hypnotic effects than midazolam (high quality evidence) [1]. Also droperidol was compared to olanzapin to induce hypnotic effects by any time point, showed no significant difference between them. This study demonstrated droperidol needed less additional medication after 60 minutes than patients received olanzapin [1].

So droperidol had more ability to calm agitated patients than placebo and haloperidol by 30 minutes after being administered [1].

Antipsychotics in the management of agitation in schizophrenia or bipolar disorder

Score of PANSS (positive and negative syndrome scale) are communicated with an additional risk of punishment and exacerbation of schizophrenia. PANSS total score of 58 is mild, PANSS of 75 is moderate and the PANSS of 95 is markedly ill, and the PANSS of 116 is severely ill [7].

Patients with schizophrenia and bipolar disorder are at higher risk of aggression and violence compared with the other psychiatric disorder [8]. Schizophrenia patient outcomes research team (PORT) considers the value of treatment approaches that can help schizophrenia patients such as antipsychotic agents, adjunctive pharmacotherapies, ECT, and psychosocial treatments. A typical antipsychotics were useful for management of acute agitation and aggression in this patients including olanzapine, ziprasidone, or aripiprazole (oral and IM injection), with or without benzodiazepine [8].

American psychiatric association (APA) recommends an antipsychotic with mood stabilizers such as lithium or valproate or Carbamazepine together with or without benzodiazepine for the control of acute agitation in bipolar patients [8]. If this treatment were insufficient, patients may benefit from ECT [8].

In the study compared the effects of IM aripiprazole with placebo in the management of agitation, there was reduction in agitation by 9.75 mg IM aripiprazole until 45 minute, whereas IM haloperidol was the same as placebo within 105 minute [8].

Previous studies have shown robust efficacy with oral aripiprazole (5 mg daily) in schizophrenia patients. Aripiprazole lauroxil is a LAI (long-acting injectable) antipsychotic (441 mg and 882 mg) which significant improvement ($p < 0.001$) was observed in aggressive patients with schizophrenia for the PANSS score [7].

Patients, who randomly received at least one dose of IM aripiprazole lauroxil, had assessed with PANSS score after administration of it. Responder to aripiprazole lauroxil was defined as $\geq 30\%$ improvement in PANSS total score at day 85. Higher dose of aripiprazole lauroxil (882 mg) has the potential benefit of greater improvement in aggressive patients [7].

Asenapine is an atypical antipsychotic that used sublingual and may control acute phase of agitation and aggression in schizophrenia and manic patients [8].

Brexpiprazole (2 mg and 4 mg) is an atypical antipsychotic with FDA approval for the treatment of bipolar and schizophrenia disorder. It is useful in the management of acute agitation and can reduce PANSS-EC score with peak plasma concentration of 4 hours [8].

Cariprazine (3-12 mg/d orally) is an atypical antipsychotic that improved the PANSS score in schizophrenia disorder [8].

Clozapine (200-625 mg/d orally) is an atypical antipsychotic that can manage aggression in schizophrenia or schizoaffective disorder [8].

In the study carried out in 2016 compared the effect

of (clozapine, 200-800 mg/d; olanzapine, 10-35 mg/d; haloperidol, 10-30 mg/d; risperidon, 4-16 mg/d) in the management of aggressive patient with schizophrenia or schizoaffective disorder, it defined that clozapine was the most effective drug in patients with the strongest symptoms of aggression, whereas olanzapine and risperidone were more effective when symptoms were milder. Haloperidol was the least effective agent [8].

Ziprasidone (orally, 80-160 mg; IM, 10-20 mg upto 40 mg) is an atypical antipsychotic drug that was used for the treatment of agitated patients [8].

Olanzapine (orally and IM) were used for the management of acute agitation in bipolar and schizophrenia disorder and reduced the PANSS-score.

Administration of antipsychotics as an IM formulation have been shown rapid onset and faster improvement compared with oral formulation, but this may create trauma to healthcare provider or patients [9].

Loxapine (10 mg) is administered by inhalation and is the first anti-agitation drug that creates rapid control of agitation. Its advantage is that administration by noninvasive route for the management of physical violence and aggression in patients with schizophrenia and bipolar disorder [9].

Rapid onset of Inhaled loxapine (with PPC: 2-3 min) is comparable with IM aripiprazole (with PPC: 1 h) [9-22].

This study demonstrated that the rapid onset of ketamine under 4 minute was comparable to haloperidol with peak plasma time of 10-20 minute. The potential advantage of ketamine includes rapid onset, preservation of airway reflexes and route of administration (both IV and IM). Inhaled loxapine have more rapid onset for the management of agitation than IM aripiprazole. Among antipsychotic drugs, sublingual asenapine, brexpiprazole, cariprazine and clozapine were effective for the treatment of acute agitation.

This paper reconciled different opposing data on cerebral metabolism and revealed key cellular and molecular nexus linking astrocyte-neuron metabolism. The astrocyte and neuron metabolic machinery is coupled to each other via calcium waves and sodium currents, mediated by signaling of glutamate and other transmitters in the tripartite synapse. Glutamate-glutamine cycling ensures cooperativity of astrocyte-neuron metabolism in accordance with the physiological requirements of the brain; however, it does not guarantee neuronal dependency on astrocyte derived lactate. Astrocyte-neurometabolic coupling is essential in normal synaptic functioning, and is critical in health and disease. Inhibitors of specific sodium and calcium channel subtypes expressed in the brain have been

found to be beneficial in certain brain diseases involving metabolic dysregulation.

CONCLUSION

The prompt management of patients with acute agitation can minimize the need for physical or mechanical restraint. Based on our study, ketamine (IM or IV) and inhaled loxapine had the most rapid onset of therapeutic effects for control of agitation and aggression in ED.

The result of this study has the potential to change treatment guidelines on clinical practice but requires further study to define their risks and benefits.

CONFLICT OF INTEREST

There is no conflict of interest regarding the publication of this paper.

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