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The evaluation of midazolam on head injured patients in the prehospital setting

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The Evaluation of Midazolam on Head Injured Patients in the Prehospital Setting

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Abstract

Midazolam (Hypnovel®) is the only sedating agent used by paramedics at St John Ambulance Service W.A. in the management of many conditions including seizure activities, antisocial or uncontrollable behaviours, back pain incidents and head injuries. Midazolam, with a rapid absorption, fast onset of action and short duration on neurological activity, has been accepted as a safe and effective agent in prehospital treatment since the late-1990s. Often, if a patient is not complying with treatment or is uncontrollable or aggressive, paramedics are required to sedate the individual. This study primarily examines the use of midazolam for the sedation of unmanageable patients who have sustained a head injury in a prehospital setting. The research investigated whether midazolam (n=49) increases the symptoms of hypotension and hypoxia in patients with head injuries in a prehospital setting. Patients that sustained a head injury but did not receive midazolam (n=47) were used as controls. Physiological parameters including blood pressure, pulse and respiration rates, oxygen saturation, along with Coma Scale and Visual Analogue Scale were placed into SPSS analysis package and Excel t-tests. Further analysis on sub divided cohorts of gender, age and severity of head injury was conducted. Results indicated that although significance differences were present, midazolam did not influence hypotension or hypoxia in head injured patients. However the nature of the head injury along with behavioural issues was the result of increased symptoms of hypotension and hypoxia.

1. Introduction

Midazolam (Hypnovel®) is the only sedating agent used by paramedics at St John Ambulance Service W.A. in the management of many conditions including seizure activities, antisocial or uncontrollable behaviours, back pain incidents and head injuries[1]. Midazolam is a member of the benzodiazepine family of drugs and is regarded as a safe alternative to opiates and barbiturates [2]. Its lipophilic properties enable rapid absorption into the brain with fast onset of action. Similar to diazepam but with a shorter duration on neurological activity, midazolam has been accepted as a safe and effective agent in prehospital treatments since the late-1990s.

Emergency medicine requires paramedics to expertly manage critical care patients, sedated patients, pain managed patients, as well as respiratory and haemodynamically compromised patients. When paramedics arrive at the scene of a severely injured or haemodynamically compromised individual the policy is to ensure the patient is delivered to hospital in a safe and stable manner. For trauma patients the policy that ensures effective transport to hospital, where appropriate treatment can begin, is to maintain minimal time at the scene of an accident and maximum treatment on route [1].

Often if a patient is not complying with treatment or is uncontrollable or aggressive, paramedics are required to sedate the individual. In the prehospital setting the last resort is to administer a sedating agent to a patient who is cerebrally hypoxic, has sustained a head injury or is agitated. However, it is considered appropriate to sedate to manage, regardless of a patients' physiological status. In other words, midazolam can be administered to a patient who is not compliant or is uncontrollable, in order for them to be transported to hospital for appropriate treatment [3].

There is a growing amount of literature suggesting that midazolam is a safe and effective sedating agent when used in a prehospital setting for seizures and agitated or psychotic patients [4-10]. However, some recent publications indicate possible negative side effects associated with midazolam and head injured patients. As Davis (2001)[11] suggests increased doses of midazolam can be associated with a detrimental outcome to patients who have sustained head injuries.

This study will primarily examine whether midazolam influences hypoxia and/or hypotension during sedation of unmanageable patients in a prehospital setting who have sustained a head injury. The majority of patients in this study had sustained a closed mild or moderate traumatic brain injury, with a small number of cases having sustained a severe traumatic brain injury (TBI).

1.2. Aims

To evaluate the effect of midazolam in patients with a head injury in the prehospital setting.

Ultimately the research will investigate whether midazolam increases the symptoms of hypotension and hypoxia in patients with head injuries in a prehospital setting.
Patients that sustained a head injury but did not receive midazolam will be used as controls.

2. Literature Review

2.1. Midazolam

The synthesis of midazolam was discovered by Fryer and Walser in 1976 [12]. Today midazolam is known by the brand names Versed®, Hypnovel® and Dormicum®. Midazolam is a Schedule 4 drug (requiring prescription) under the Poisons Act 1964 (WA). Hypnovel® is the brand of midazolam used by paramedics at St John Ambulance Service W.A. Midazolam is a short acting benzodiazepine that induces sedation, hypnosis, amnesia and anaesthesia with the effects on the CNS depending on the dose received, the route of administration and the presence or absence of other medications. After intravenous administration at a dose of 5 to 10mg, onset of sedation will occur within 2 to 3 minutes, followed by peak sedation for the individual at 30-60 minutes following injection [13]. Midazolam has been known to cause an anaesthetic state among individuals. However, 14% of patients will not reach anaesthetic state with the use of midazolam alone [14].

2.1.1. History of the implementation of midazolam in prehospital care in Australia.

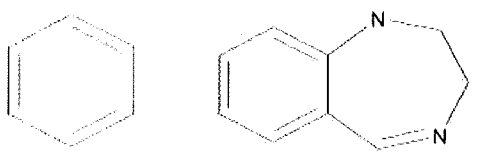
Midazolam (Hypnovel®, Roche) has many clinical uses and has been used not only for its sedative actions, but for the management of seizure activity, back pain and antisocial or aggressive behaviours in prehospital settings. From the beginning of April 1997 NSW paramedics began using midazolam in the prehospital setting as it was found to produce equal clinical effects to those of diazepam, a commonly used sedative, with fewer complications of respiratory depression in patients. Moreover, midazolam has a half life of 2-3 hours compared to a half life of 6 hours for diazepam making midazolam a more appropriate drug to use in prehospital care [7]. Thus midazolam provides patients with fast acting treatment without prolonged sedation [13].

Midazolam was first introduced as a sedating agent at St John Ambulance Service W.A. for the management of fits or seizure activity in 1999. In 2003 midazolam was implemented as a sedating agent for antisocial or aggressive behaviours in the prehospital setting. By 2004 midazolam was also introduced as a pain management tool for back pain symptoms [15-17]. Prior to that midazolam's primary use was as a sedative agent during minor surgical procedures in hospital care. Midazolam is now widely

accepted as a safe drug, not only in hospital settings but for the management of seizures, back pain and antisocial or aggressive behaviours in Western Australian prehospital settings [18].

2.1.2. The chemical structure of Midazolam

Midazolam belongs to the class of benzodiazepines. The term benzodiazepine derives from its chemical structure, a benzene ring fused to a diazepine ring (Figure 1). Another important feature of benzodiazepines is the addition of a halogen on the benzene ring, which contributes to the drugs ability to become electron attracting [19].



Benzene 1,4-Benzodiazepine

Figure1. A structural diagram of a benzene ring and a 1,4-benzodiazepine compound [12].

The distinguishing component of benzodiazepines is the seven-membered diazepine ring of carbon and nitrogen atoms fused to the benzene ring. When there is one nitrogen incorporated into the seven-membered ring it is known as azepine. When two nitrogens are incorporated it is known as a diazepine ring. Thus, the name 1,4-diazepine evolved [12]. Various modifications within the 1,4-diazepine region have yielded various benzodiazepine compounds with similar binding characteristics and similar modes of action [19]. Midazolam also has an imidazole ring fused to the 1,4-diazepine ring making the drug more lipophilic with low solubility in water and the shortest-acting of the benzodiazepines compounds (Figure 2). The basic nitrogen at position 2 of the imidazole ring enables the active agent (1-hydroxylmidazolam) to form water-soluble salts with acids to produce a stable injection solution for intramuscular administration [20].

Another important component of the benzodiazepine chemical structure is a second benzene ring system attached to position 5 of the 1,4-diazepine ring. This ultimately gives rise to the name 5-aryl-1,4-benzodiapine, the 5-aryl ring enhances the potency of the drug [12]. Another halogen, fluorine provides the benzodiazepine structure with further electron-attracting ability (Figure 2).

The structure of midazolam is 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4] benzodiazepine (Figure 2.) and the chemical formula is $C_{18}H_{13}ClFN_3$. The compound has a molecular weight of 325.8 and in its non active state it is a solid white or yellowish crystal [21].

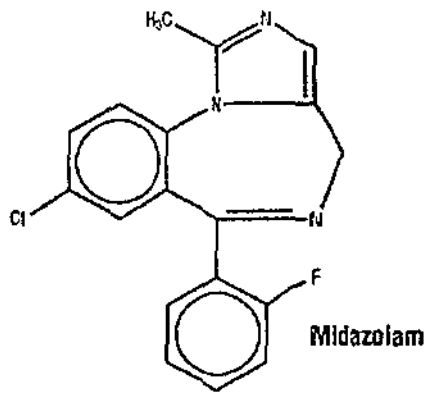


Figure 2. A structural illustration of midazolam [22].

Midazolam manufactured for injection is a clear colourless or faint yellow solution that contains midazolam as a salt together with sodium chloride in sterile water. At a pH between 2.9 and 3.7 each prepared injection is available in 1mg/ml and 5mg/ml strengths.

2.1.3. Dosage and Administration of Midazolam

The dosage of midazolam administered to patients varies depending on the patient's symptoms (Table 1). The preferred route of administration of midazolam in the prehospital setting is intramuscular. Intramuscular administration has been shown to be an easier and safer form of administration for fitting or aggressive patients [7]. After intramuscular administration the onset of midazolam effects will occur within 1 to 5 minutes. The time of onset will vary for each individual and will depend on the rate of absorption from muscle. The onset of midazolam effects is also strongly dependent on an individual's genetic makeup, particularity to the genes coding for drug metabolising ability [23-27].

Table 1. Dosage of midazolam used for patients in prehospital setting [28]

	Adult Dose of Midazolam mg
Seizures	10mg if frail or over 65 – half adult dose
Antisocial	10-25mg
Back Pain	2.5-5mg

Midazolam is absorbed by as much as 80 to 100% following intramuscular administration and according to Dundee *et al* (1984)[13] produces greater sedation, more amnesia, a significant antianxiety effect and less pain at the injection site compared to hydroxyzine or diazepam.

It is important to mention that emergency situations are based on rapid assessment and administration of treatment, hence weight is not considered by the W.A. Ambulance Service Clinical Practice Guidelines (see appendix 1) and doses administered to patients are not based on the patient's weight.

2.1.4. Primary Indications of Midazolam in the Prehosptial Setting

The two primary indications of the use of midazolam in W.A. prehospital setting are for seizure activity and anti-social or unmanageable behaviour. There is a growing amount of literature that suggests that midazolam is an acceptable sedating agent used in prehospital care to treat acute seizure activity in patients [4, 5, 7, 9]. The study conducted by Rainbow *et al* (2002)[7] suggested that midazolam is more effective than diazepam in controlling seizures in children in a prehospital setting. The study demonstrated that there were significantly fewer cases of respiratory depression when midazolam was used compared to diazepam. Also the mean dosage of midazolam administered to patients was significantly less than that of diazepam [7].

A separate study conducted by McGlone and Smith (2001)[5] indicated that intranasal midazolam (0.2mg) is more effective and less invasive than intravenous diazepam for treatment of seizure in children in emergency care. Harbord *et al* (2004)[9] also found that (0.2-0.3mg) intranasal midazolam is more effective and easier to administer than rectal

diazepam for children with acute seizures in the community setting. Moreover, the overall time for cessation of seizures in children is quicker with the use of intranasal midazolam (0.2mg/kg) than with intravenous diazepam (0.3mg/kg) [4]. Shah *et al* (2005)[10] also suggests that intramuscular midazolam (0.2mg/kg) is safer and more effective than intravenous diazepam (0.2mg/kg) in the control of seizures irrespective of the type of convulsion and age of the child. Ultimately these studies found that midazolam is safe and easy to administer and the time to treat seizures is reduced compared to diazepam.

The second most common use of midazolam is for the treatment of aggressive or unmanageable behaviours in patients that may be due to severe illness such as mental illness, substance misuse or head injuries. If the patient cannot be calmed by words, sedation of the patient may be unavoidable. There are studies that suggest midazolam is a safe and effective sedating agent for the control of anti-social or aggressive patients in prehospital care[6]. The TREC (Text REtrieval Conference) Collaborative Group[8] found that administering 7.5mg to 15mg of midazolam consistently sedated aggressive or agitated patients for up to two hours. Although haloperidol and promethazine were also used in this study intramuscular administration of midazolam was clearly more effective with minimal adverse effects [8]. Huf *et al* (2002)[6] agrees that there are few adverse effects associated with the use of intramuscular administration of midazolam in agitated or violent patients. The dosage of midazolam used in the study by Huf *et al* (2002)[6] varied from 3-10mg depending on the clinical condition of the patient and previous exposure to other drugs.

2.1.5. Contraindications and side effects of Midazolam

While there are many studies that support the safety and efficacy of midazolam when used as a sedating agent, there are several side effects which include respiratory depression as the most concerning [29-31]. Early studies conducted by Dundee *et al* (1984)[13] suggest that intravenous midazolam causes a decrease in tidal volume that is compensated for by an increase in respiratory rate. A benzodiazepine antagonist flumazenil can reverse the respiratory complications and sedation induced by midazolam [6, 8, 32].

Other side effects or minor adverse reactions in patients after intramuscular administration of midazolam include: headaches (1.3%) and/or local effects at the injection site (pain (3.7%), indurations (0.5%), redness (0.5%) and muscle stiffness (0.3%) [33]. On rare occasions midazolam provokes hostility and violence instead of calming effects in patients [32]. Other adverse reactions reported with intramuscular administration of midazolam are given in Table 2.

Table 2. Adverse Reactions of Intramuscular Administration of Midazolam [33]

Complication	Type of Reaction
Respiratory	Laryngospasm, bronchospasm, dyspnoea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnoea.
Cardiovascular	Bigeminy, premature ventricular contractions, tachycardia, nodal rhythm, cardiovascular collapse, vasovagal episode, cardiac arrest.
Gastrointestinal	Acid taste, excessive salivation, retching.
CNS/Neuromuscular	Anterograde amnesia, headache, euphoria, confusion, argumentativeness, nervousness, agitation, anxiety, grogginess, irritability, restlessness, emergence delirium or agitation, prolonged emergence from anaesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, tonic/clonic movements, muscle tremor, involuntary movements, athetoid movements, dizziness, ataxia, dysphoria, slurred speech, dysphonia, paraesthesia.
Ophthalmic	Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, difficulty in focusing
Dermatologic	Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, erythema, rash, pruritus.
Miscellaneous	Yawning, lethargy, chills, weakness, continued phonation, ears blocked, loss of balance, light-headedness, toothache, faint feeling, haematoma.

2.1.6. Pharmacology and Mechanisms of Action of Midazolam

The structure of midazolam provides it with lipophilic properties allowing the drug to cross lipid membranes, particularly the blood-brain barrier and affect the Central Nervous System (CNS) [2]. Midazolam is also known to act on peripheral nervous tissue, resulting in coronary vasodilation and neuromuscular blockages at very high doses [19].

Midazolam like benzodiazepines has an affect on the CNS. There is a scarcity of literature available on the specific regions of the CNS that are affected by midazolam. However the mechanism of action of midazolam in general on the CNS is via binding to the gamma-aminobutyric acid (GABA) receptor. GABA is a naturally occurring neurotransmitter found in the CNS [2, 34]. The GABA receptors, membrane bound proteins, are divided into two major subtypes: $GABA_A$ and $GABA_B$ receptors [19]. $GABA_A$ receptors induce sedation and anti-anxiety effects and are located in the cerebellum and spinal cord of the CNS [35]. $GABA_B$ receptors are located in the basal ganglia and hippocampus. These receptors are associated with muscle relaxation as well as memory and learning.

Midazolam binds to the $GABA_A$ receptor, resulting in physiological effects such as sedation, decreased anxiety, amnesia, muscle relaxation, anaesthesia and anticonvulsant activity [2]. This area of interest requires more research and is continually being investigated.

2.1.7. The $GABA_A$ receptor complex

The $GABA_A$ receptor complex belongs to a large family of hetero-oligomeric ligand-gated ion channels. The ionotropic $GABA_A$ receptor is composed of five known subunits that contain recognition sites for various chemical agents. The $GABA_A$ receptor complex contains recognition sites for; GABA agonists and antagonists, a barbiturate binding site, a benzodiazepine binding site, a steroid binding site and a picrotoxin binding site (Figure 3) [12]. Ultimately the binding of midazolam to its recognition site results in an increased influx of chlorine ions, which result in hyperpolarisation at the post-synaptic membrane and inhibition of neurotransmission [36].

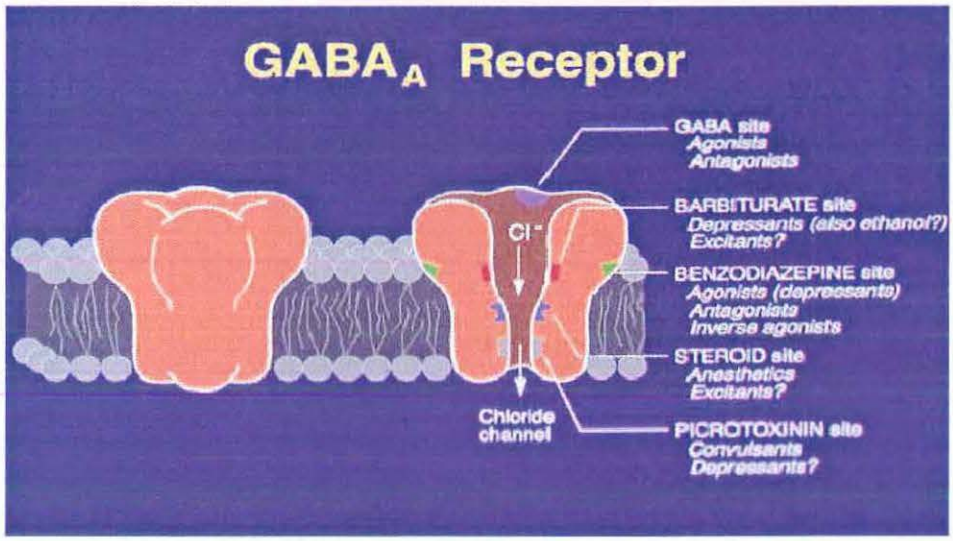


Figure 3. An illustration of the $GABA_A$ receptor complex, showing recognition sites for GABA, barbiturate, benzodiazepine, steroid and picrotoxinin [12].

Benzodiazepines are known to modulate the binding of GABA to the $GABA_A$ receptor ultimately altering binding in an allosteric fashion [12]. Benzodiazepines can act as agonists (positive modulators), inverse agonists (negative modulators) or as antagonists (blocking both positive and negative modulators), depending on the benzodiazepine compound and the subunit composition of various $GABA_A$ receptor isoforms [37, 38]. Benzodiazepine agonists binding to the $GABA_A$ receptor site will increase chlorine ion influx and inverse agonists will decrease chlorine ion flow. Midazolam acts as a positive agonist displaying inhibitory functions when binding at the $GABA_A$ receptor site [23].

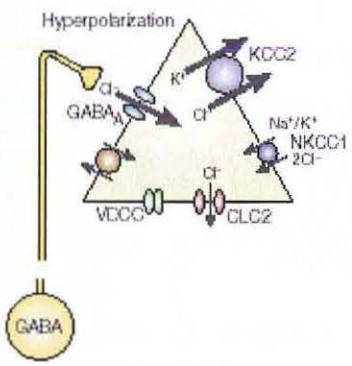


Figure 4. A schematic diagram of hyperpolarisation activity during inhibition of GABA [38].

When midazolam binds to the $GABA_A$ receptor there is an influx of chlorine ions resulting in hyperpolarisation activity of the cell membrane (Figure 4) [38]. Ultimately the influx of chorine ions suppresses neuron activity at specific neurons in the CNS resulting in sedation or relaxation of the individual.

2.1.8. Metabolism of Midazolam via cytochrome P450 Drug Metabolising Enzymes

Midazolam is predominately metabolised by the hepatic cytochrome P450 drug metabolising system. Mammalian cytochrome P450 proteins (CYP450) are a group of haem-thiolate monooxygenases that play a major role in drug metabolism. Cytochrome P450 enzymes act via an NADPH-dependent electron transport pathway and have the ability to form multiple interactions with a variety of xenobiotic compounds [39]. The name 'cytochrome P450' is derived from the absorbance spectrum of the haem containing protein, characterised by a maximum absorption wavelength of 450nm when reduced in the presence of carbon monoxide (CO) [40]. The P in CYP450 stands for pigment hence the abbreviation, P450 [40, 41].

Midazolam is one such drug that is metabolised by cytochrome P450. Many studies suggest that CYP450 enzymes contribute to 70 -90% of the metabolism of midazolam in individuals [26, 27]. P450 proteins are categorised into families, subfamilies and single cytochrome P450 enzymes. There are 18 families (CYP1-18) and 43 subfamilies (CYPX1-2) of cytochrome P450 found in humans [40]. The predominant form of cytochrome P450 is CYP3A, clustered on chromosome 7. Many of these proteins are expressed in liver tissue, intestinal epithelium and the kidney [42, 43]. The major role of CYP450 enzymes is to catalyse the phase I reaction of drug metabolism which involves oxidation, reduction or hydroxylation reactions, to modify the xenobiotic, making it more easily excreted. *In vivo* studies show that four members of the CYP3A subfamily contribute to midazolam clearance in the body; CYP3A4, CYP3A5, CYP3A7 and CYP3A43 [27, 41].

Being a water soluble compound midazolam is carried via transport proteins in the blood to the liver where it is metabolised to less active metabolites. During the first phase of metabolism midazolam is hydroxylated by CYP450 into three metabolites; 1-hydroxymidazolam (1-OHM) (responsible for 63% of midazolam activity), 4-hydroxymidazolam (inactive) and 1-hydroxymidazolam glucuronide (1-OHMG) (6% of midazolam activity) [39, 43-45]. The production of 1-OHM is the predominant pathway of

midazolam metabolism accounting for 95% of the process, with only 5% metabolised to 4-hydroxymidazolam [45].

Genetic variations in human population groups exhibit various polymorphisms. Polymorphisms with CYP450 genes that code for the multiple enzymes are thought responsible for a large proportion of genetic variation in drug metabolism ability and sensitivity to drugs. A variation in drug metabolising ability determines whether individuals are good or poor metabolisers of alcohol or other drug agents [46]. This area of research is not completely understood and requires further investigation.

2.2. What are the causes of Head Injuries in W.A?

Midazolam is commonly used by paramedics to treat unmanageable patients who have sustained a mild or moderate head injury. The different head injuries assessed within this study include: fractures, lacerations, abrasions, swelling, bleeding, tenderness or contusions.

Road trauma accidents are a growing concern for community and health departments in the state of W.A. There was a 26.4% increase in the number of head injury admissions to Royal Perth Hospital (RPH) from 2003 to 2004. The 2004 RPH Trauma Registry Report states that 48% of admissions of major traumas are a result of road accidents. Of this group, 25% of cases sustained head injuries in a motor vehicle accident. Other major causes of head injuries in W.A. were; 38% as a result of a fall, 21% struck by an object, 6% were involved in motor bike accidents, 3% as pedestrians, 3% as pedal cyclists, 1% were sporting or recreational accidents, 1% were gunshot or stabbing accidents and 1% were horse riding accidents [47].

In 2004 85% of major trauma admissions to RPH were via ambulance transportation, escorted by a St John Ambulance paramedic. Management of patients with head injuries is important to ensure minimisation of secondary brain injury. Management and prevention of secondary brain injury must begin at the scene of the accident. To ensure sufficient management and prevention of secondary brain injury early detection of injury, rapid transportation to hospital and resuscitation to prevent deterioration in the patient are required by the paramedics [48 49].

The Brain Injury Association of W.A. Inc states: "*Brain Injury is not a disease, or something you can "catch". Brain Injury is defined as a loss of brain function, caused by accidents, poisoning, stroke, brain tumours, infections or lack of oxygen* [50]"
(Table 3).

Table 3. Causes of Head Injuries [50]

Cause	Description
Accidents	Road accidents, Sport and/or work related, assaults, shaking your child.
Poisoning	Drinking to much alcohol, overuse of prescribed drugs, use of illegal drugs, petrol and chemical sniffing.
Stroke	Rupture of a blood vessel in the brain, blockage of blood supply to the brain
Brain tumours	Cancerous or non-cancerous
Infections	Meningitis, Encephalitis
Lack of oxygen	Near drowning, severe asthma attack, lack of blood flow to the brain (heart attack).

2.2.1. How is the brain injured?

Traumatic brain injury (TBI) is a major problem with both high mortality and high morbidity. Almost 2% of Australians have acquired head injuries with resulting disabilities [50]. Injury to the brain may occur at the time of injury (primary injury) and/or subsequently due to cerebral ischaemia (secondary injury). Hypotension and hypoxemia are causes of secondary brain injury. Many studies have confirmed that outcomes following traumatic brain injuries result in individuals experiencing cognitive and behavioural symptoms days, weeks even months after the trauma. Ranging symptoms may include headaches, vertigo, sensitivity to bright lights and/or noise, blurred vision, insomnia, restlessness, reduced concentration and memory problems, irritability, fatigue, anxiety and depression [51-57]. When brain injury has occurred it is crucial for prehospital management to focus on preventing secondary brain injury and minimising the chances of a poor outcome [49, 58, 59].

Paramedics at St John Ambulance encounter many incidents of head injured patients. The majority of patients in this study have sustained a mild or moderate TBI. Mild or moderate TBI may involve the head being injured as a result of a fractures, lacerations, abrasions, swelling, bleeding, tenderness or contusions.

2.2.2. Glasgow Coma Scale (GCS)

The Glasgow coma scale (GCS) is the most widely used scoring system in assessment of the level of consciousness for patients with head injuries in a prehospital situation. The Glasgow coma scale score provides a simple measure of patients' level of consciousness with a high degree of reliability. It is simple and easy to use; its observations are based on eye response, verbal response and motor response (Table 4). The Glasgow coma scale score provides paramedics with an assessment tool for patients' conscious state which enables satisfactory management of the p. ients' injuries prior to hospital admission.

Table 4. Glasgow Coma Score table [3]

Eye Opening (E)	**Verbal Response (V)**	**Motor Response (M)**
4 = Spontaneous	5 = Normal Conversation	6 = Normal
3 = To voice	4 = Disorientated conversation	5 = Localised to pain
2 = To pain	3 = Words, but not coherent	4 = Withdraws to pain
1 = None	2 = No words, only sounds	3 = Decorticate posture
	1 = None	2 = Decerebrate
		1 = None
		Total = E+V+M

2.2.3. Mild Traumatic Brain Injury

A mild traumatic brain injury can be defined by any of the following: (1) Direct contact to the head, due to outside forces or to acceleration/deceleration trauma (falls). (2) Loss of consciousness (LOC) experienced by the individual is usually brief, lasting seconds to minutes, and in some cases no loss of consciousness is experienced; only a dazed consciousness occurs. (3) The patient's evaluated GCS is 13 to 15. Only a GCS score of 15 represents a true mild TBI. (4) Confusion along with amnesia is experienced by the patient lasting minutes to a few hours, whether or not there are periods of unconsciousness. (5) No focal signs are present in the patient; the patient may also have a pale complexion, be diaphoretic and experience nausea or be ataxic [60 61].

2.2.4. Moderate Traumatic Brain Injury

A Moderate Traumatic Brain Injury (TBI) has a GCS grading of 9 to 13. Moderate TBI, like mild TBI, can result in the head being injured from fractures, lacerations, abrasions, amnesia or contusions. Individuals with a moderate TBI pose a greater risk of developing secondary brain injury. Fifty percent of moderate TBI patients suffer long-term disabilities [62].

2.2.5. Severe Traumatic Brain Injury

A severe TBI has a GCS score of less than 9. The causes of severe TBI are identical to those of mild TBI, with the exceptions of whiplash and assaults that occur more commonly with mild TBI [60]. Severe TBI occurs from considerable forces exceeding the skulls tolerance; the greater the force the greater the injury. This may include a fracture, laceration, abrasion, amnesia or contusion, however to a greater degree of severity. Other indicators of severe TBI may be continual brain stem reflex posturing, increased intracranial pressure (ICP), hypertension and increased body temperature [63].

2.2.5.1. Skull Fractures/Direct Head Injury

Skull fractures are often categorised as basilar, linear, depressed or comminuted skull fractures that are either open or closed. Skull fractures are often the result of a force that penetrates or fractures the skull, causing the skull to bend inwards at the site of impact and at the same time curve outwards around the site of impact [64]. Direct head injuries that result in fractures may occur during a motor vehicle accident, falls or assaults i.e. direct strikes to head.

Fractures to the head can also occur at the base of the skull (Anterior fossa fractures). An anterior fossa fracture increases damage to cranial nerves and vessels that result in rhinorrhea or epistaxis (cerebrospinal fluid drainage from the nose), periorbital ecchymosis and anosmia (cranial nerve one damage) or visual defects (cranial nerve two damage). Injuries involving the middle ear are a result of posterior fossae fractures. Fractures to the temporal petrous bone can result in blood drainage from the ear [63].

2.2.5.2. Dislocations/Indirect Head Injury

Indirect head injury involves injury to brain tissue as a result of severe whiplash or "shaken baby syndrome". This form of trauma to the brain results in disruption of nerve cells and their axons leading to permanent brain damage or complications [65].

2.2.5.3. Contusions/Swelling/Diffuse Axonal Injury

Diffuse axonal injury causes brain tissue damage that is often difficult to detect and is often the cause of indirect head injury. The nerve cells located in grey matter of the brain communicate with the white matter, axon nerve tracts. Sudden stretching, twisting or jolting of these nerve tracts can lead to coma or brief loss of consciousness. Diffuse axonal injury results in microscopic damage to brain tissue that can not be visualised on Computer Tomograph (CT) or Magnetic Resonance Angiography (MRA) scans but may appear on a Single Photon Emission Computed Tomography (SPECT) scan [65].

2.2.5.4. Hypoxic/Anoxic Head Injury

The brain weighs approximately 2% of our body weight, yet consumes 20% of the body's oxygen supply. Therefore, the brain is more susceptible to injury if there is insufficient oxygen supply. Hypoxic brain injury is a decreased supply of oxygen to the brain and anoxic brain injury is the absolute lack of oxygen. Injury to the brain will often set in after a lack of blood flow to the brain and is also known as ischaemic insult [66].

The areas of the brain affected by reduced oxygen supply include the cerebral and cerebellar regions, in particular basal ganglia. Regions of the brain that are also sensitive to lack of oxygen include the Purkinje fibres of the cerebellum and parieto-occipital cortex and the hippocampus [66].

2.2.5.5. Secondary Types of Head Injuries

Secondary brain injury is often the result of the head being injured minutes, hours or days after the initial insult. The cause of this type of injury will vary from intracranial haematomas, intracranial infection, epilepsy and systemic hypoxia to hypotension. The most common secondary brain injuries sustained by patients in this study are intracranial haematomas.

2.2.5.6. Intracranial Haematomas

An intracranial haematoma is a localised collection of blood due to a tissue injury or tearing of blood vessels. The dura is membrane that covers the brain and spinal cord. Blood clots that develop between the skull and dura mater are known as epidural haematomas. A blood clot that develops between the dura mater and the brain is called a subdural haematoma [50].

There are a number of intracranial haematomas identified in the brain all arising from various physiological complications. These haematomas may be located in various regions of the brain: Frontal, parietal, temporal, occipital, optic nerve, cerebella-pontine angle, brain stem, hypothalamic and pituitary, posterior fossa [66].

Only patients that sustained a closed skull fracture and a GCS between 14 & 15 (mild TBI) 9 to 13 (moderate TBI) and a GCS < 9 (severe TBI) were used in this study, with the majority having sustained a mild to moderate TBI.

2.3. Pathophysiology of Head Injuries

Fundamental processes occur during head injuries which can culminate in cell death. These processes include the release of the excitotoxic amino acids, aspartate and glutamate, production of free radicals, and increased levels of lactate and hydrogen ions. The final pathway of the process involves the entry of calcium ions into the cells, which results in cell swelling. Swelling within the cranium results in an increase in intracranial pressure (ICP) and a reduction in cerebral perfusion pressure (CPP = the mean arterial blood pressure - intracranial pressure). What follows is cerebral ischaemia and reduced delivery of oxygen and glucose to the tissue, provoking further acidosis and the release of free radicals [67]. Studies have shown that brain ischaemia is the predominant cause of complicating traumatic brain injury [68-71].

2.3.1. Hypoxia and Hypotension in Head Injuries

Injury to the CNS in head trauma leads to a chain of physiological events that lead to secondary brain damage. Insufficient oxygen supply to the brain after injury to the head is known to result in deleterious effects. Inadequate oxygen to brain tissue may occur from arterial hypotension, low haemoglobin concentration and decreased oxygen saturation. Most of these factors are the result of secondary brain damage that occurs from extracranial injuries, causing respiratory failure and blood loss [72].

The treatment of hypoxemia and hypotension often occur at the scene of injury. Ventilation of the patient ensures that both hypoxemia and hypotension are controlled prior to patient arrival at hospital. A decrease in oxygen saturation of less than 90% suggests the patient has reached a hypoxemic state, (oxygen saturation (PO_2) measures of less than 60 mmHg are defined as hypoxic). Studies by Godwin *et al* (2005) [30] have shown that benzodiazepines and opioids used in sedation and analgesia increase the patient's chances of developing hypoxemia. Chestnut *et al* (1993) [73] reported that hypoxia occurs in 45.6% of severely head-injured patients and has a significant influence on patient mortality.

Hypotension is a lowering of blood pressure; a systolic blood pressure of less than 90 mm Hg. [46] In a recent article Choi *et al* (2004) [74] found that doses of 0.2-0.3mg of midazolam caused hypotension in 20% of intubated patients in a prehospital setting. Rapid administration and increased doses of midazolam may also be associated with hypotension [30]. Many studies have suggested that midazolam causes arterial hypotension, especially in elderly and haemodynamically comprised individuals [74-76]. The biochemical mechanisms behind midazolam-induced hypotension are not completely understood. However, discussion by Jones *et al* (1979) [77] and Reves *et al* (1984) [78] suggest that the negative inotropic effects, reduced vascular resistance [79, 80] or reduced sympathetic activity [81] may account for midazolam-induced hypotension. Moreover other studies suggest that midazolam directly relaxes vessel tone and causes arterial hypotension [82 75, 83].

This study will examine the relationship between midazolam use in a prehospital setting for patients with head injuries. There will be particular focus on whether midazolam contributes to increased symptoms of hypoxia and hypotension.

There is a growing amount of literature that suggests midazolam contributes to increased symptoms of hypoxia and hypotension in individuals. The study by Chestnut *et al* (1993) [73] clearly showed that hypoxia and hypotension lead to an increase in mortality of 50% in patients suffering from severe head injuries. This raises an important question; if midazolam contributes to increased hypoxia and hypotension in patients, why is midazolam being administered to individuals who have sustained head injuries when hypoxemia and hypotension are common complications associated with head injured patients? Therefore, this study will be assessing whether midazolam does increase the symptoms of hypoxia and hypotension in patients with head injuries.

2.3.2. Glasgow Coma Scale Assessment for Traumatic Brain Injuries in the prehospital setting

Western Australian paramedics use the Glasgow Coma Scale (GCS) to categorise the severity of Traumatic Brain Injury (TBI) in individuals. A mild TBI can include fractures, lacerations, abrasions or contusions. More commonly mild TBI patients include loss of consciousness (LOC), amnesia, vomiting, headaches or changes in mental status at the time of trauma (Figure 5). A GCS score of 13 to 15 is used to categorise a mild TBI [62]. A mild head injury is often subdivided into categorises of low risk, medium risk or high risk [84].

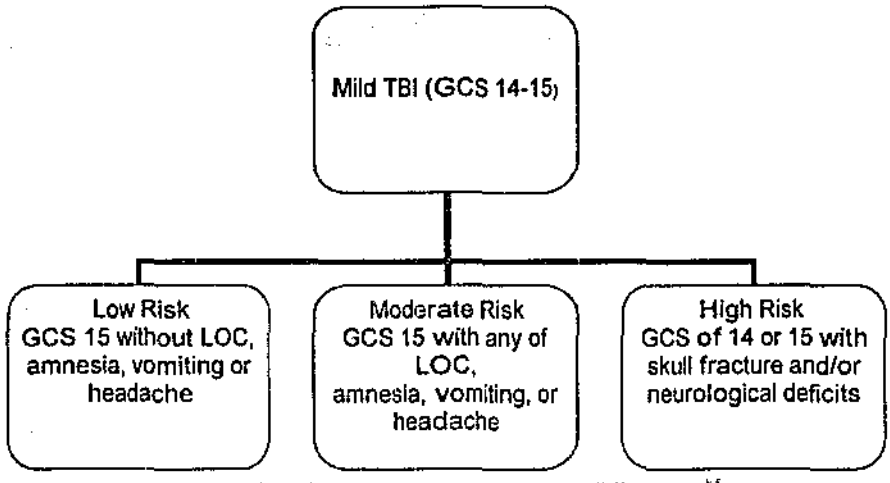


Figure 5. Algorithm of categories of Mild TBI (GCS) scores [85].

2.3.3. Patient Assessment in the prehospital setting

Any assessment of TBI management in a prehospital setting requires a valid tool. The visual analogue scale (VAS) and verbal numerical response scale (VNRS) are two valid assessment tools used by paramedics at St John Ambulance Service W.A. These tools ensure a quick, simple, reliable and valid assessment of patient's injuries.

2.3.3.1. Visual Analogue Scale (VAS)

The visual analogue scale consists of a vertical or horizontal line, 10cm in length with scales of no pain and worst pain at each end (Table 5). The respondents mark a point on the line to represent the intensity of his or her pain. The VAS simplicity, reliability and validity allow the pain assessment tool as an optimal device for describing pain levels for patients [86]. The limitation surrounding the accuracy of the VAS tool is that some individuals may be visually impaired, suffer from motor deficits or cognitive impairment. This may occur particularly in elderly individuals or trauma cases. The other limitation found with the VAS is the error rate within the scale of approximately 20mm [87].

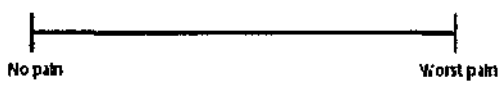


Figure 6. An example of a visual analogue scale [88]

2.3.3.2. Verbal Numerical Response Scale (VNRS)

The VNRS has the broadest application in the prehospital setting. Paramedics ask the patient to describe the severity of their pain on a scale from zero (no pain) to ten (most severe pain). The patients' level of pain is recorded and treatment is administered where appropriate [87].

Limitations surrounding both the VAS and VNRS tools are that individual interpretations of pain intensity and severity will vary slightly. However both these tools are used for assessment of traumatic brain injury in a prehospital setting and appropriate assessment is necessary to ensure effective treatment [89].

3. Methods

The patient cohort comprises retrospective data collected from (unidentified) patient care records between January 2001 and February 2006 from the database at St John Ambulance Service W.A. (see appendix 1 - Patient Care Record sample sheet). Patient care records for all cases that were treated with midazolam and sustained a head injury were used and compared to patient care records of cases that had sustained a head injury, but did not receive midazolam. The patients that did not receive midazolam (non-midazolam) for treatment was used as the control group in this study.

Ethical approval for the project was given by Edith Cowan University Ethics Committee. St John Ambulance Service W.A. also gave permission for the use of unidentified patient care records to conduct the research.

Physiological parameters were taken from patient care records to assess whether midazolam influences hypoxia or hypotension in head injured patients and a comparison of these physiological parameters was made with patients who had sustained a head injury and did not receive midazolam (see appendix – 2).

The data parameters collected from patients care records for quantitative multivariate analysis included:

1. Age
2. Gender
3. Glasgow Coma Scale (GCS) which determines classification of head injury. Mild TBI = 15 to 14 GCS, moderate TBI = 9 to 13 GCS and severe TBI = < 9 GCS
4. Systolic Blood Pressure [initial reading (SBP1) & final reading (SBP2)]
5. Pulse Rate per minute [initial reading (PR1) & final reading (PR2)]
6. Respiration Rate per minute [initial reading (RR1) & final reading (RR2)]
7. Oxygen Saturation in mm Hg [initial reading ($PaO_2$1) & final reading ($PaO_2$2)]

Each physiological parameter SBP1, PR1, RR1 and $PaO_2$1 was recorded by paramedics on arrival at the scene during initial assessment of patient and prior to administration of midazolam or for the non-midazolam cases (control group) parameters were recorded by paramedics on arrival at the scene during initial assessment of the patient. The final reading for each physiological parameter, SBP2, PR2, RR2, $PaO_2$2, was recorded by

paramedics approximately 5-10 minutes after initial administration of midazolam or for the non-midazolam cases approximately 5-10 minutes after initial assessment.

Hypotension in the individual was determined after midazolam administration where systolic blood pressure (SBP) decreases to 90 mm Hg or less with an initial SBP greater than 90 mmHg. Other variables considered include where a further decrease in SBP of 5 mmHg or more in patients is observed with an initial SBP higher than 90 mmHg. Where SBP cannot be obtained other indicators of hypotension (decreased pulse rate and respiration rate) were tabulated and examined.

To determine whether a patient has reached a hypoxemic state, pulse oximetry is used to measure oxygen saturation. A decrease in oxygen saturation of less than 90% suggests the patient has reached a hypoxemic state [30]. Readings of less than 60 PO_2 mmHg will designate hypoxia. Where readings of oxygen saturation cannot be obtained, respiratory distress in the patient was tabulated and utilised for this study.

Statistical comparisons of the parameters were undertaken using the Statistical Package for the Social Sciences (SPSS) software version 14 (SPSS Incorporated Inc.). Analyses were conducted on the study population and subsequent analysis was conducted by dividing the study population into categories of gender (male and female), age (less than 35 years and over 35 years) and head injuries (mild TBI, moderate TBI and severe TBI).

Data was inserted into the SPSS spread sheet with the following parameters recorded; age, gender, category of TBI, whether patients had received treatment of midazolam or no treatment, patients systolic blood pressure readings prior to treatment (initial reading), patients systolic blood pressure after treatment (final reading). For the patients that did not receive treatment the initial readings were recorded as initial and final PaO_2 reading, initial and final pulse rate readings, initial and final respiration rate readings.

A box plot test was used to determine normality between physiological data sets (see appendices 3 to 30). All data was normally distributed, hence Independent Sample Tests, Levenes's Test for Equality of Variances and Paired Sample T-Test comparisons were used to determine statistical significance between pairs of physiological

parameters; SBP1-SBP2, PR1-PR2, RR1-RR2 and $PaO_2$1-$PaO_2$2. Additional analysis was conducted on mild TBI, moderate TBI and severe TBI using Microsoft Excel Students t-test. Significance was determined with one-tailed distribution and paired two-sample equal/unequal variance.

The main limitation of the study was the difficulty in obtaining pre-midazolam physiological measures from treated patients. Where a patient is uncontrollable or aggressive, obtaining measures of pulse rate, blood pressure or oxygen saturation values is extremely difficult if not impossible. In a situation like this the paramedics' primary concern is to sedate the individual so no further injury to the patient or anyone else occurs. Therefore records of patients' initial physiological measures, immediately prior to the administration of midazolam, may result in restricted data validity. Another limitation was incomplete patient care records. Limiting the study to complete patient care records including the above criteria severely restricted the number of cases for the study and minimised the study population from 4500 to 96.

3.1. Methods for Analysis of Results

The analysis conducted in this study included the following:

1. An analysis of whether midazolam influences hypotension in patients with a head injury. The physiological parameters used to determine symptoms of hypotension are systolic blood pressure, respiration rate and pulse rate.

2. Analysis of whether midazolam influences hypoxia in patients with a head injury was determined by using the physiological parameter oxygen saturation.

The approaches used to determine these outcomes were:

a) A statistical comparison between the initial reading for midazolam and non-midazolam was conducted. The variables used to determine whether there is a significant difference between initial midazolam and initial non-midazolam are: systolic blood pressure (SBP1), respiration rate (RR1) and pulse rate (PR1).

b) An analysis for significant difference between the initial and final SBP1-SBP2, RR1-RR2 and PR1-PR2 readings for the midazolam cohort.

c) An analysis for significant difference between the initial and final SBP1-SBP2, RR1-RR2 and PR1-PR2 readings for the non-midazolam cohort.

d) A comparison of the statistical significant difference for the final SBP2, $PaO_2$2, PR and RR readings between the midazolam and non-midazolam cohorts.

e) An analysis for significant difference between b) and c) was conducted. Is there is significant difference between the initial and final readings for midazolam compared to the initial and final readings for the non-midazolam cohort.

3.1.1. Patient cohorts

The study population includes a total of 96 patients. The majority of patients had sustained a mild to moderate head injury. The study population included a total of 56 patients with a mild TBI, 25 patients with a moderate TBI and 15 patients categorised as suffering from severe TBI (Table 5). Of the 96 patients, 49 received midazolam for sedating purposes and 47 patients were not treated with midazolam. The 47 patients not treated with midazolam were used as the control group.

Table 5. Number of cases for each category of TBI for midazolam and non-midazolam cohorts

	Mild TBI	Moderate TBI	Severe TBI	Total
midazolam	19	16	14	49
	38.8 %	32.7 %	28.6 %	100 %
non-midazolam	37	9	1	47
(control)	78.7 %	19.1 %	2.1 %	100 %
Total	56	25	15	96
	58.3 %	26 %	15.6 %	100 %

The total number of males and females for the study included 52 males and 44 females. The number of males and females in the study population for the midazolam cohort consisted of 34 males and 15 females. In the non-midazolam cohort there were a total of 18 males and 29 females (Table 6).

Table 6. The number of males and females in the study population

	male	female	Total
midazolam	34	15	49
	69.4 %	30.6%	100 %
non-midazolam	18	29	47
(control)	38.3%	61.7 %	100 %
Total	52	44	96
	54.2 %	45.8 %	100 %

The number of cases in each age group is provided in table 7. For the midazolam cohort the majority of patients were between the ages of 16-25yrs (21.3%), 26-35yrs (27.7%) and 36-45yrs (23.4%). In the non-midazolam cohort, the majority of patients (38.3%) were 66yrs and older. There were two patients where the age group was not recorded by paramedics.

Table 7. Age Demographics of the Study Population

	1-10yrs	11-15yrs	16-25yrs	26-35yrs	36-45yrs	46-55yrs	56-65yrs	66yrs older	Total
midazolam	0	0	10	13	11	5	1	7	47
	0 %	0 %	21.3%	27.7%	23.4%	10.6%	2.1%	14.9%	100%
non-midazolam (control)	1	2	9	5	3	2	7	18	47
	2.1%	4.3%	19.1%	10.6%	6.4%	4.3%	14.9%	38.3%	100%
total	1	2	19	18	14	7	8	25	94
	1.1%	2.1%	20.2%	19.1%	14.9%	7.4%	8.5%	26.6%	100%

4.0. Results

4.1 Analysis of Midazolam/Non midazolam cohorts

4.1.1 Statistical analysis of systolic blood pressure

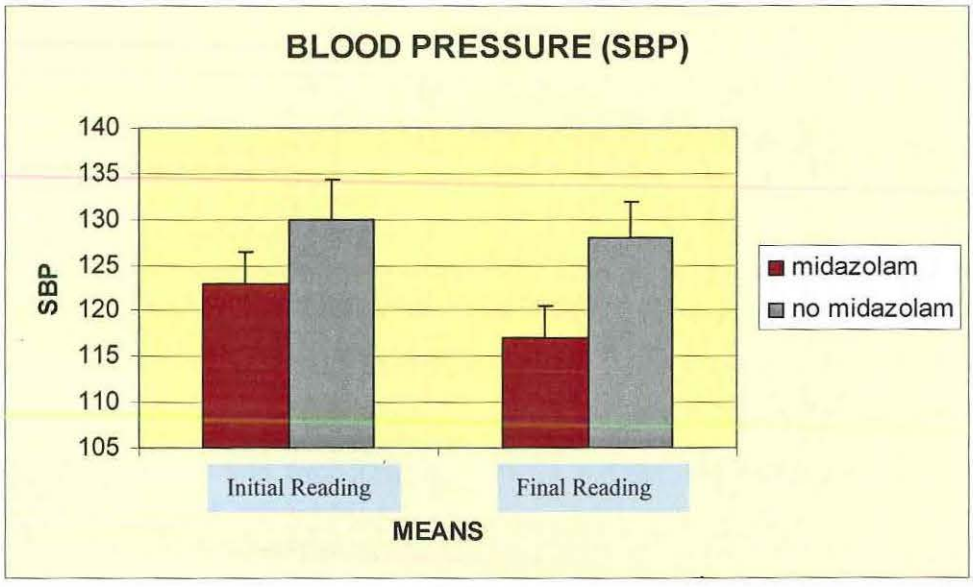


Figure 7. Means and Standard Error of Blood Pressure (SBP) for midazolam and non-midazolam groups

Table 8. SBP summary of means ± SE for midazolam and non-midazolam cohort

	Initial Reading (SBP1)	Final Reading (SBP2)	Mean decrease (SBP1-SBP2)	Sig. (p)
Midazolam (n = 49)	123 ± 3.4	117 ± 3.5	5.5 ± 2.45	0.029
no midazolam (n = 47)	130 ± 4.4	128 ± 3.9	2.2 ± 0.86	0.015

Error bar = ± SE (Standard Error) of the mean

The mean decrease between SBP1-SBP2 in patients for the midazolam cohort is 5.5 ± 2.45, compared to a mean decrease of 2.2 ± 0.86 in SBP1-SBP2 for the non-midazolam cohort. When comparing the statistical differences between these means there is no statistical significance between the mean SBP decrease of the midazolam cohort to the mean SBP decrease of the non-midazolam cohort.

a) When a comparison was made to determine whether a significant difference was present between the initial SBP for the midazolam and non-midazolam cohorts (not shown in table format); $p = 0.150$ (as calculated by the SPSS Levene's Test for equality of variances). When $p < 0.05$ there is a statistical significant difference between these

groups. Hence, there is no significant difference between the initial SBP readings for midazolam and non-midazolam cohorts.

b) When comparing the significant difference between the initial and final SBP reading for the midazolam cohorts; $p = 0.029$. When $p < 0.05$ there is a statistical significant difference between these groups. In this case there is a statistical significant difference between the initial reading (SBP1) and final reading (SBP2) for the midazolam cohorts. The final SBP reading is significantly ($p < 0.05$) lower than the initial SBP reading.

c) When comparing the significant difference between the initial and final SBP reading for the non-midazolam cohort; $p = 0.015$ when $p < 0.05$ there is statistical difference between these groups. In this case there is a statistical significant difference between the initial reading (SBP1) and final reading (SBP2) for the non-midazolam cohorts. The final reading is significantly ($p < 0.05$) lower than the initial reading.

d) When comparing the statistical significant difference for the final SBP reading between the midazolam and non-midazolam cohorts; $p = 0.035$ when $p < 0.05$ there is a significant difference between the two groups. Therefore, there is a significant ($p < 0.05$) difference between the final SBP reading for the midazolam and non-midazolam cohorts.

e) When a comparison was made between the differences for SBP1-SBP2 for the midazolam and non-midazolam cohorts i.e. the statistical difference between the differences $p = 0.076$; when $p > 0.05$ there is no statistical significance between the initial and final SBP reading between the midazolam and non-midazolam cohorts. i.e. there is no statistical significant difference between the differences b) and c).

4.1.1. Statistical Analysis of Oxygen Saturation (PaO_2)

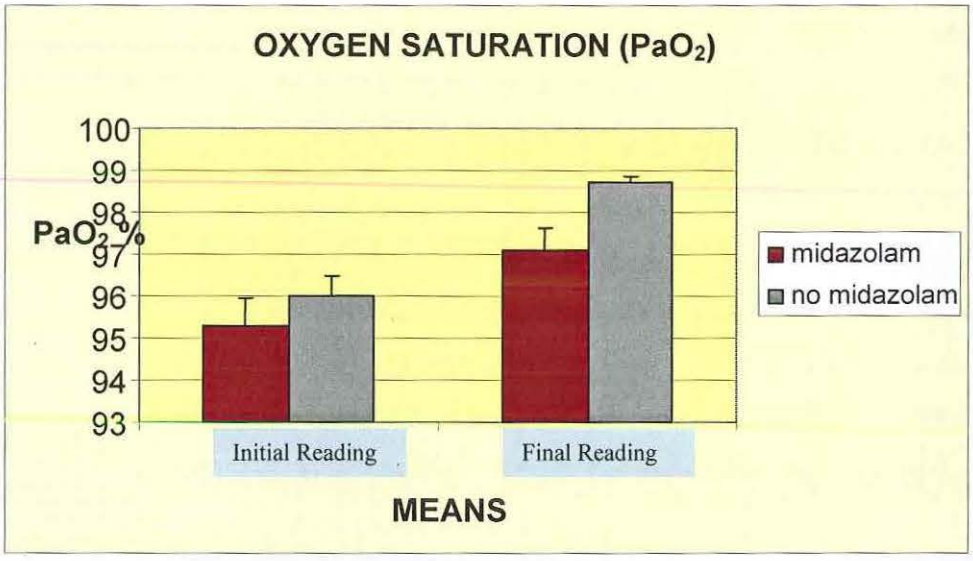


Figure 8. Means of Oxygen Saturation for midazolam and non-midazolam groups

Table 9. PaO_2 summary of means ± SE for midazolam and non-midazolam cohort.

	Initial Reading ($PaO_2$1)	Final Reading ($PaO_2$2)	Mean increase ($PaO_2$1- $PaO_2$2)	Sig. (p)
midazolam (n = 49)	95.3 ± 0.7	97.1 ± 0.5	1.8 ± 0.472	0.000
no midazolam (n = 47)	96 ± 0.5	98.7 ± 0.2	2.6 ± 0.443	0.000

Error bar = ± SE (Standard Error) of the mean

The mean PaO_2 increase for the midazolam cohort is 1.8 ± 0.472 after treatment with midazolam. The treated patients mean PaO_2 readings do not reach 98%. For the non-midazolam cohort there is a 2.6 ± 0.443 increase in PaO_2. Both midazolam and no midazolam patients received oxygen supplementation during treatment. When comparing the statistical differences between these means there is a statistical significance between the mean PaO_2 increase of the midazolam cohort to the mean PaO_2 increase of the non-midazolam cohort.

a) When comparing the significant difference between the initial PaO_2 for both midazolam and non-midazolam cohorts (not shown in table format); $p = 0.394$ (as calculated by the SPSS Levene's Test for equality of variances). When $p > 0.05$ there is no statistical significant difference between these groups. Therefore, no significant

difference between the initial PaO_2 readings for midazolam and non-midazolam cohorts was seen.

b) When comparing the significant difference between the initial and final PaO2 reading for the midazolam cohorts; $p = 0.000$ when $p < 0.05$ there is a statistical significant difference between theses groups. In this case there is a statistical significant difference between the initial reading ($PaO_2 1$) and final reading ($PaO_2 2$) for the midazolam cohorts. The final reading is significantly ($p < 0.05$) higher than the initial reading.

c) When comparing the significant difference between the initial and final PaO_2 reading for the non-midazolam cohort; $p = 0.000$ when $p < 0.05$ there is statistical difference between these groups. In this case there is a statistical significant difference between the initial reading ($PaO_2 1$) and final reading ($PaO_2 2$) for the non-midazolam cohorts. The final reading is significantly ($p < 0.05$) higher than the initial reading.

d) When comparing the statistical significant difference for the final PaO_2 reading between the midazolam and non-midazolam cohorts. Using Independent Samples T-Test, Levene's test for Equality of Variance, equal variances assumed, $p = 0.010$ when $p < 0.05$ there is a significant difference between the two groups. Therefore, there is a significant ($p < 0.05$) difference between the final PaO_2 reading for the midazolam and non-midazolam cohorts.

e) A statistical comparison between $PaO_2 1$-$PaO_2 2$ midazolam and $PaO_2 1$-$PaO_2 2$ non-midazolam cohorts; $p = 0.009$ when $p < 0.05$ there is a statistical significance between the initial and final PaO_2 reading between the midazolam and non-midazolam cohorts. i.e. there is a statistical significant difference between the differences b) and c).

4.1.3. Statistical Analysis of Respiration Rate

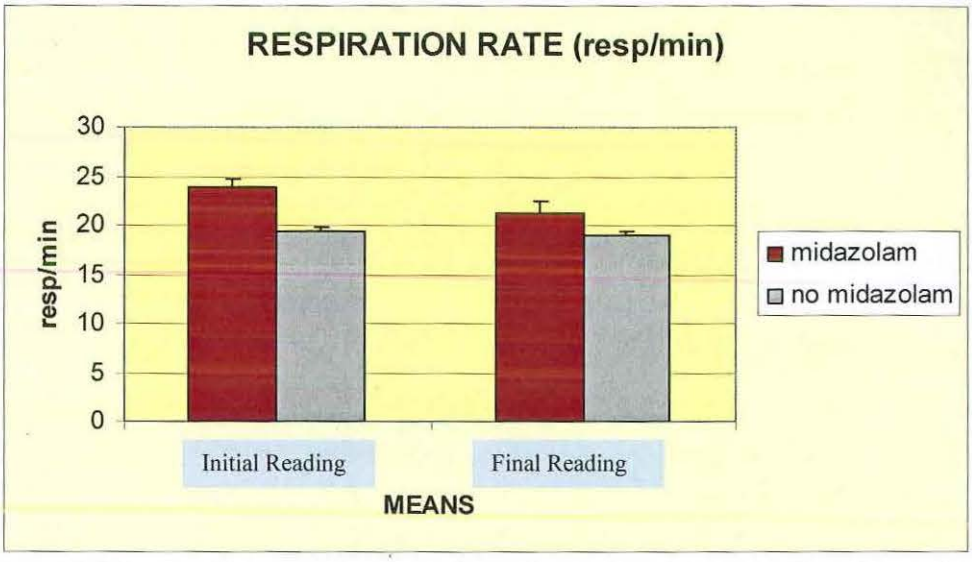


Figure 9. Means of Respiration Rate for midazolam and non-midazolam cohorts

Table 10. Respiration Rate summary of means ± SE for midazolam and non-midazolam cohort.

	Initial Reading (RR1)	Final Reading (RR2)	Mean decrease (RR1-RR2)	sig. (p)
midazolam (n = 49)	23.8 ± 1.0	21.3 ± 1.1	2.5 ± 0.929	0.009
no midazolam (n = 47)	19.4 ± 0.5	18.9 ± 0.4	0.425 ± 0.171	0.017

Error bar = ± SE (Standard Error) of the mean

The mean decrease for the midazolam cohort is 2.5 ± 0.929 resp per min after midazolam administration. Whereas, the mean decrease for the non midazolam cohort is 0.425 ± 0.171 resp/min with no treatment administered. When comparing the statistical differences between these means there is no statistical significant difference between the mean RR decrease for the midazolam cohort to the mean RR decrease for the non-midazolam cohort.

a) When comparing the statistical significant difference for initial Respiration Rate (RR1) between midazolam and non-midazolam cohorts (not shown in table format); $p = 0.000$ (as calculated by the SPSS Levene's Test for equality of variances). When $p < 0.05$ there is a statistical significant difference between the groups. In this case there is a significant difference between the initial RR1 readings for midazolam and the initial RR1 reading non-midazolam cohorts.

b) When comparing the significant difference between the initial and final RR reading for the midazolam cohorts; $p = 0.009$ when $p < 0.05$ there is a statistical significant difference between the groups. In this case there is a statistical significant difference between the initial reading (RR1) and final reading (RR2) for the midazolam cohorts. The final reading is significantly ($p < 0.05$) lower than the initial reading.

c) When comparing the significant difference between the initial and final RR reading for the non-midazolam cohort; $p = 0.017$ when $p < 0.05$ there is a statistical difference between the groups. In this case there is a statistical significant difference between the initial reading (RR1) and final reading (RR2) for the non-midazolam cohorts. The final reading is significantly ($p < 0.05$) lower than the initial reading.

d) When comparing the statistical significant difference for the final RR reading between the midazolam and non-midazolam cohorts; $p = 0.064$ when $p > 0.05$ there is no significant difference between the two groups. Therefore, there is no significant ($p > 0.05$) difference between the final (RR2) reading for the midazolam and final (RR2) reading for non-midazolam cohort.

e) When comparing the differences between RR1-RR2 midazolam and RR1-RR2 non-midazolam cohorts $p = 0.316$ when $p > 0.05$ there is no statistical significance between the initial and final RR reading between midazolam and non-midazolam cohorts, i.e. there is no statistical significant difference between the differences b) and c).

4.1.4. Statistical Analysis of Pulse Rate

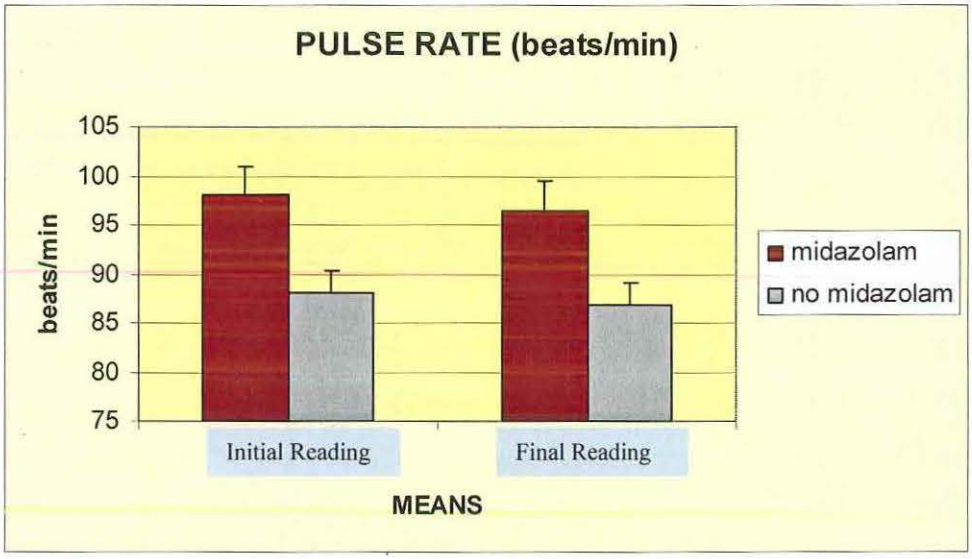


Figure 10. Means of Pulse Rate for midazolam and non-midazolam cohorts

Table 11. Pulse Rate summary of means ± SE for midazolam and non-midazolam cohort

	Initial Reading (PR1)	Final Reading (PR2)	Mean decrease (PR1-PR2)	sig. (p)
Midazolam (n = 49)	98.1 ± 2.7	96.4 ± 3.1	1.7 ± 1.7	0.338
no midazolam (n = 47)	88.1 ± 2.2	86.9 ± 2.2	1.1 ± 0.814	0.173

Error bar = ± SE (Standard Error) of the mean

The mean decrease in pulse rate (beats/min) for the midazolam cohort is 1.7 ± 1.7 after midazolam administered. Whereas, the mean decrease in pulse rate for the non-midazolam cohort is 1.1 ± 0.814. When comparing the statistical differences between these means there is no statistical significant difference between the mean PR decrease for the midazolam cohort to the mean PR decrease for the non-midazolam cohort.

a) When comparing the significant difference between the initial Pulse Rate (PR) for both midazolam and non-midazolam cohorts (not shown in table format); $p = 0.006$ (as calculated by the SPSS Levene's Test for equality of variances). When $p < 0.05$ there is a statistical significant difference between the groups. In this case there is a significant difference between the initial PR readings for midazolam and initial PR for non-midazolam cohorts.

b) When comparing the significant difference between the initial and final PR reading for the midazolam cohorts; $p = 0.338$ when $p > 0.05$ there is no statistical significant

difference between the groups. In this case there is no statistical significant difference between the initial reading (PR1) and final reading (PR2) for the midazolam cohorts.

c) When comparing the significant difference between the initial and final PR reading for the non-midazolam cohort; $p = 0.173$ when $p > 0.05$ there is no statistical difference between the groups. In this case there is no statistical significant difference between the initial reading (PR1) and final reading (PR2) for the non-midazolam cohorts.

d) When comparing the statistical significant difference between the final PR reading for the midazolam and non-midazolam cohorts; $p = 0.014$ when $p < 0.05$ there is a significant difference between the two groups. Therefore, there is a significant ($p < 0.05$) difference between the final PR reading for the midazolam and non-midazolam cohorts.

e) When comparing the differences for PR between midazolam and non-midazolam cohorts; $p = 0.939$ when $p > 0.05$ there is no statistical significance between the initial and final PR reading between the midazolam and non-midazolam cohorts. i.e. there is no statistical significant difference between the differences b) and c).

4.2. Analysis of Gender & Midazolam/Non-midazolam

4.2.1. Statistical analysis of gender vs. systolic blood pressure

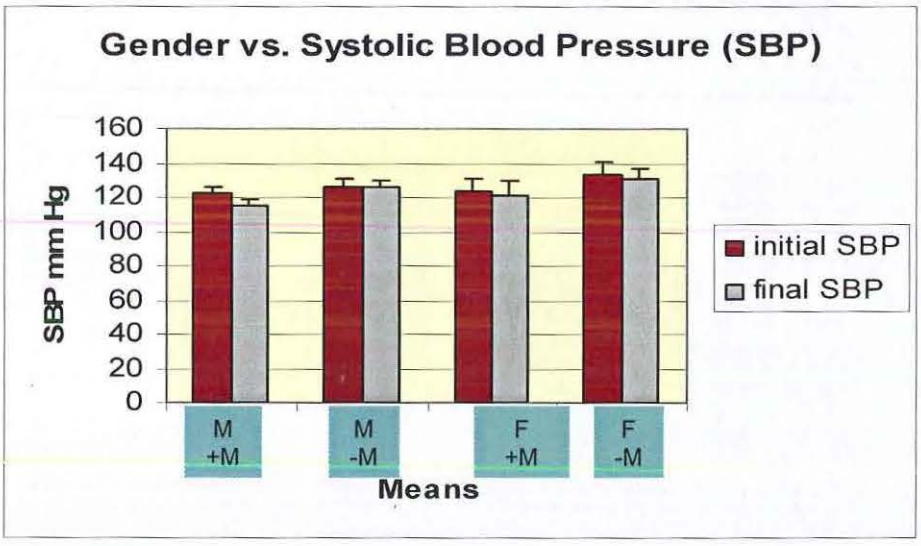


Figure 11. Means of Blood Pressure (SBP) for males and females

Table 12. Systolic Blood Pressure summary of means and ±SE for gender

Gender vs. Systolic Blood Pressure (SBP)	a) Initial SBP Reading +M & -M	b) Difference between Initial & Final SBP reading +M	c) Difference between Initial & Final SBP reading -M	d) Final SBP Reading +M & -M	e) Statistical Difference between b) & c)
MALES n=52	+M =122.7 SE ±3.44 -M =126.5 SE ±4.67 Mean difference 3.82 ±5.8 **p = 0.514** no significance	I = 122.7 SE ± 3.44 F = 115.5 SE ±3.56 Mean decrease 7.2 ±3.28 **p = 0.035** yes significant	I = 126.5 SE ± 4.67 F = 125.8 SE ±4.32 Mean decrease 0.72 ±3.28 **p = 0.709** no significance	+M =115.5 SE ±3.56 -M =125 SE ±4.32 Mean difference 10.3 ±5.83 **p = 0.083** no significance	**p = 0.079** no significance
FEMALES n=44	+M= 123.3 SE ±8.15 -M= 133.6 SE ±6.51 Mean difference 10.29 ±10.8 **p = 0.346** no significance	I = 123.3 SE ± 8.15 F = 121.8 SE ±8.33 Mean decrease 1.5 ±2.7 **p = 0.579** no significance	I = 133.6 SE ± 6.52 F = 130.5 SE ±5.85 Mean decrease 3.1 ±1.23 **p = 0.018** yes significant	+M =121.8 SE ±8.33 -M =130.5 SE ±5.85 Mean difference 10.3 ±5.83 **p = 0.393** no significance	**p = 0.798** no significance

+M = midazolam
-M = no midazolam
I = initial reading
F = final reading
p = significance value
SE± = Standard error mean
M = males
F = females

4.2.2. Statistical analysis of gender vs. oxygen saturation

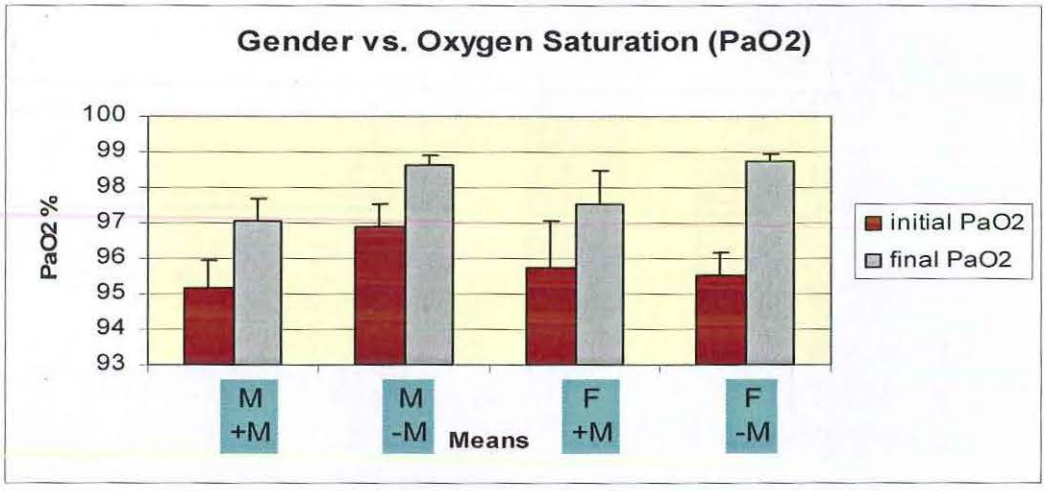


Figure 12. Means of Oxygen Saturation for males and females

Table 13. Oxygen Saturation summary of means and ±SE for gender cohort

Gender vs. Oxygen Saturation (PaO_2)	a) Initial PaO_2 Reading +M & -M	b) Difference between Initial & Final PaO_2 reading +M	c) Difference between Initial & Final PaO_2 reading -M	d) Final PaO_2 Reading +M & -M	e) Statistical Difference between b) & c)
MALES n=52	+M =95.1 SE ±0.789 -M =96.9 SE ±0.661 Mean difference 1.74 ±1.18 **p = 0.149** no significance	I = 95.1 SE ± 0.789 F = 97 SE ±0.665 Mean increase 1.88 ±3.71 **p = 0.006** yes significant	I = 96.9 SE ± 0.661 F = 98.6 SE ±0.269 Mean increase 1.72 ±0.516 **p = 0.006** yes significant	+M =97 SE ±0.666 -M =98.6 SE ±0.269 Mean difference 1.58 ±0.939 **p = 0.033** yes significant	**p = 0.343** no significance
FEMALES n=44	+M =95.7 SE ±1.33 -M =95.5 SE ±0.654 Mean difference 0.216 ±1.31 **p = 0.870** no significance	I = 95.7 SE ± 1.33 F = 97.5 SE ±0.955 Mean increase 1.8 ±0.579 **p = 0.008** yes significant	I = 95.5 SE ± 0.653 F = 98.7 SE ±0.202 Mean increase 3.24 ±0.625 **p = 0.000** yes significant	+M =97.5 SE ±0.955 -M =98.7 SE ±0.202 Mean difference 1.22 ±0.977 **p = 0.343** no significance	**p = 0.798** no significance

+M = midazolam
-M = no midazolam
I = initial reading
F = final reading
p = significance value
SE± = Standard error mean
M = males
F = females

4.2.3. Statistical analysis of gender vs. respiration rate

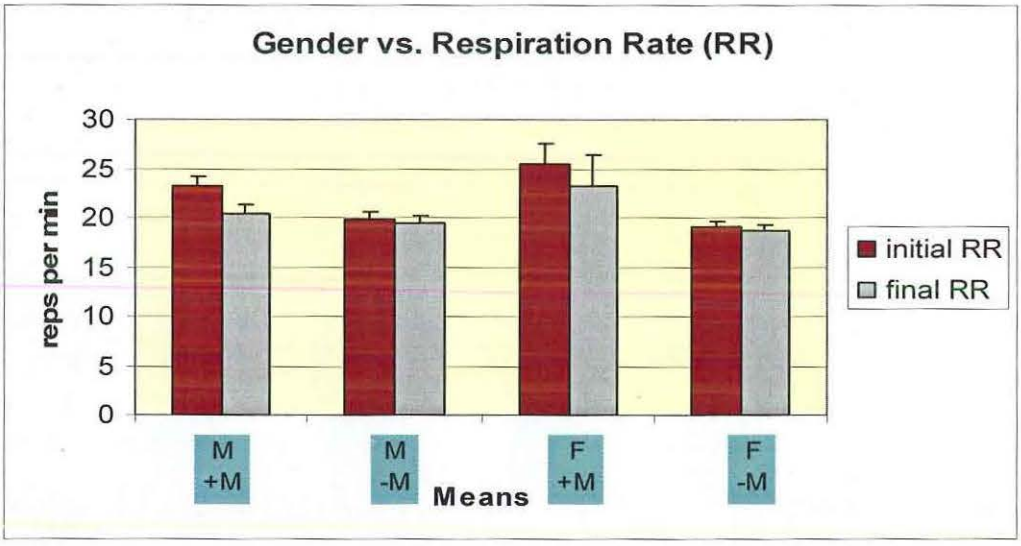


Figure 13. Means of Respiration Rate for males and females

Table 14. Respiration Rate summary of means and ±SE for gender

Gender vs. Respiration Rate (RR)	a) Initial RR Reading +M & -M	b) Difference between Initial & Final RR reading +M	c) Difference between Initial & Final RR reading -M	d) Final RR Reading +M & -M	e) Statistical Difference between b) & c)
MALES n=52	+M =23.1 SE ±1.09 -M =19.8 SE ±0.766 Mean difference 3.26 ±5.93 **p = 0.018** yes significant	I = 23.1 SE ± 1.09 F = 20.4 SE ±0.963 Mean decrease 2.71 ±0.942 **p = 0.007** yes significant	I = 19.9 SE ± 0.766 F = 19.4 SE ±0.755 Mean decrease 0.444 ±0.304 **p = 0.163** no significance	+M =20.4 SE ±0.963 -M =19.4 SE ±0.755 Mean difference 0.997 ±1.22 **p = 0.419** no significance	**p = 0.479** no significance
FEMALES n=44	+M =24.4 SE ±2.14 -M =19.1 SE ±0.608 Mean difference 6.29 ±1.74 **p = 0.012** yes significant	I = 25.4 SE ± 2.14 F = 23.3 SE ±3.09 Mean decrease 2.13 ±2.22 **p = 0.353** no significance	I = 19.1 SE ± 0.608 F = 18.7 SE ±0.518 Mean decrease 0.415 ±0.208 **p = 0.056** no significance	+M =23.3 SE ±3.09 -M =18.7 SE ±0.518 Mean difference 4.57 ±2.32 **p = 0.165** no significance	**p = 0.439** no significance

+M = midazolam
-M = no midazolam
I = initial reading
F = final reading
p = significance value
SE± = Standard error mean
M = males
F = females

4.2.4. Statistical analysis of gender vs. pulse rate

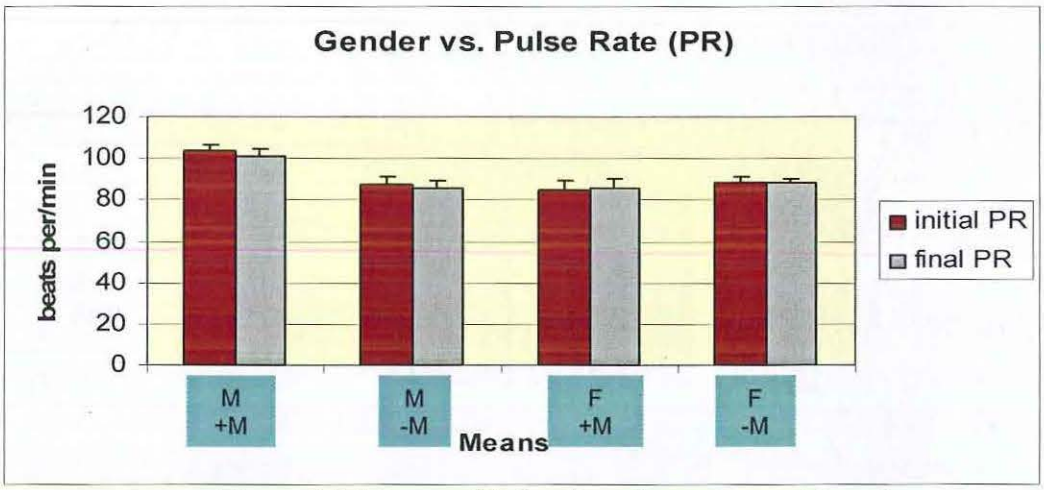


Figure 14. Means of Pulse Rate for males and females

Table 15. Pulse Rate summary of means and ±SE for gender

Gender vs. Pulse Rate (PR)	a) Initial PR Reading +M & -M	b) Difference between Initial & Final PR reading +M	c) Difference between Initial & Final PR reading -M	d) Final PR Reading +M & -M	e) Statistical Difference between b) & c)
MALES n=52	+M =103.8 SE ±3.03 -M =87.2 SE ±3.88 Mean difference 16.7 ±5.03 **p = 0.002** yes significant	I = 103.8 SE ± 3.03 F = 101.3 SE ±3.62 Mean decrease 2.53 ±2.02 **p = 0.218** no significance	I = 87.2 SE ± 3.89 F = 85.3 SE ±3.79 Mean decrease 1.88 ±1.21 **p = 0.136** no significance	+M =20.4 SE ±0.963 -M =19.4 SE ±0.755 Mean difference 0.997 ±1.22 **p = 0.007** yes significant	**p = 0.952** no significance
FEMALES n=44	+M =85.2 SE ±4.28 -M =88.7 SE ±2.76 Mean difference 3.46 ±4.92 **p = 0.486** no significance	I = 85.2 SE ± 4.28 F = 85.5 SE ±5.16 Mean increase 0.267 ±3.39 **p = 0.938** no significance	I = 88.6 SE ± 2.8 F = 88.0 SE ±2.65 Mean decrease 0.655 ±1.09 **p = 0.554** no significance	+M =20.4 SE ±0.963 -M =19.4 SE ±0.755 Mean difference 0.997 ±1.22 **p = 0.630** no significance	**p = 0.847** no significance

+M = midazolam
-M = no midazolam
I = initial reading
F = final reading
p = significance value
SE± = Standard error mean
M = males
F = females

4.3. Analysis of Age & Midazolam/Non-midazolam

4.3.1. Statistical analysis of age vs. systolic blood pressure

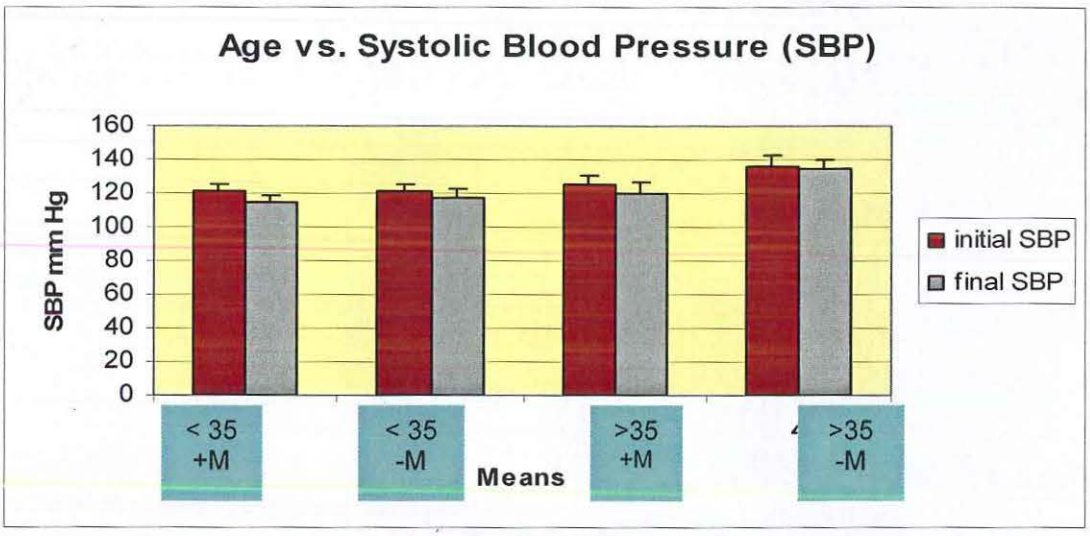


Figure 15. Means of Systolic Blood Pressure for age categories

Table 16. Systolic Blood Pressure summary of means and ±SE for age categories

Age vs. Systolic Blood Pressure (SBP)	a) Initial SBP Reading +M & -M	b) Difference between Initial & Final SBP reading +M	c) Difference between Initial & Final SBP reading -M	d) Final SBP Reading +M & -M	e) Statistical Difference between b) & c)
<35yrs n=40	+M =121.1 SE ±4.63 -M =120.8 SE ±4.23 Mean difference 0.248 ±6.5 **p = 0.970** no significance	I = 121.1 SE ± 4.63 F = 114.9 SE ±4.07 Mean decrease 6.2 ±2.52 **p = 0.022** yes significant	I = 120.9 SE ± 4.23 F = 118 SE ±4.05 Mean decrease 2.88 ±1.06 **p = 0.015** yes significant	+M =114.9 SE ±4.06 -M =118 SE ±4.06 Mean difference 3.09 ±5.88 **p = 0.603** no significance	**p = 0.253** no significance
>35yrs n=54	+M =125.9 SE ±5.28 -M =136.6 SE ±6.27 Mean difference 10.65 ±8.46 **p = 0.214** no significance	I = 125.9 SE ± 5.28 F = 120.4 SE ±6.08 Mean decrease 5.5 ±4.34 **p = 0.218** no significance	I = 136.5 SE ± 6.27 F = 134.7 SE ±5.48 Mean decrease 1.8 ±1.22 **p = 0.151** no significance	+M =120.4 SE ±6.08 -M =134.8 SE ±5.48 Mean difference 14.3 ±8.19 **p = 0.086** no significance	**p = 0.194** no significance

+M = midazolam
-M = no midazolam
I = initial reading
F = final reading
p = significance value
SE± = Standard error mean

4.3.2. Statistical analysis of age vs. oxygen saturation

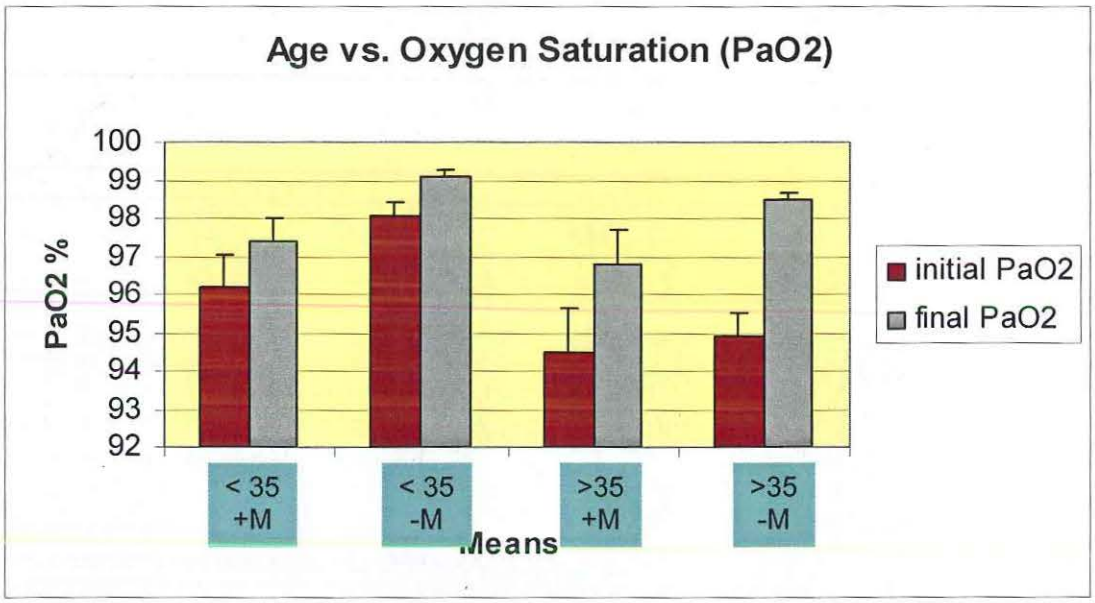


Figure 16. Means of Oxygen Saturation for age categories

Table 17. Oxygen Saturation summary of means and ±SE for age categories

Age vs. Oxygen Saturation (PaO_2)	a) Initial PaO_2 Reading +M & -M	b) Difference between Initial & Final PaO_2 reading +M	c) Difference between Initial & Final PaO_2 reading -M	d) Final PaO_2 Reading +M & -M	e) Statistical Difference between b) & c)
<35 yrs n=40	+M =96.2 SE ±0.831 -M =98.1 SE ±0.358 Mean difference 1.88 ±0.036 **p = 0.046** yes significant	I = 96.2 SE ± 0.831 F = 97.4 SE ±0.615 Mean increase 1.2 ±0.426 **p = 0.009** yes significant	I = 98.1 SE ± 0.358 F = 99.1 SE ±0.168 Mean increase 1.06 ±0.290 **p = 0.002** yes significant	+M =97.4 SE ±0.615 -M =99.1 SE ±0.168 Mean difference 1.73 ±0.732 **p = 0.024** yes significant	**p = 0.170** no significance
>35 yrs n=54	+M =94.5 SE ±1.11 -M =94.9 SE ±0.642 Mean difference 0.400 ±1.22 **p = 0.745** no significance	I = 94.5 SE ± 1.11 F = 96.8 SE ±0.936 Mean increase 2.29 ±0.842 **p = 0.012** yes significant	I = 98.1 SE ± 0.358 F = 99.1 SE ±0.168 Mean increase 3.56 ±0.290 **p = 0.000** yes significant	+M =96.8 SE ±0.936 -M =98.5 SE ±0.223 Mean difference 1.67 ±0.963 **p = 0.094** no significance	**p = 0.042** yes significant

+M = midazolam
-M = no midazolam
I = initial reading
F = final reading
p = significance value
SE± = Standard error mean

4.3.3. Statistical analysis of age vs. respiration rate

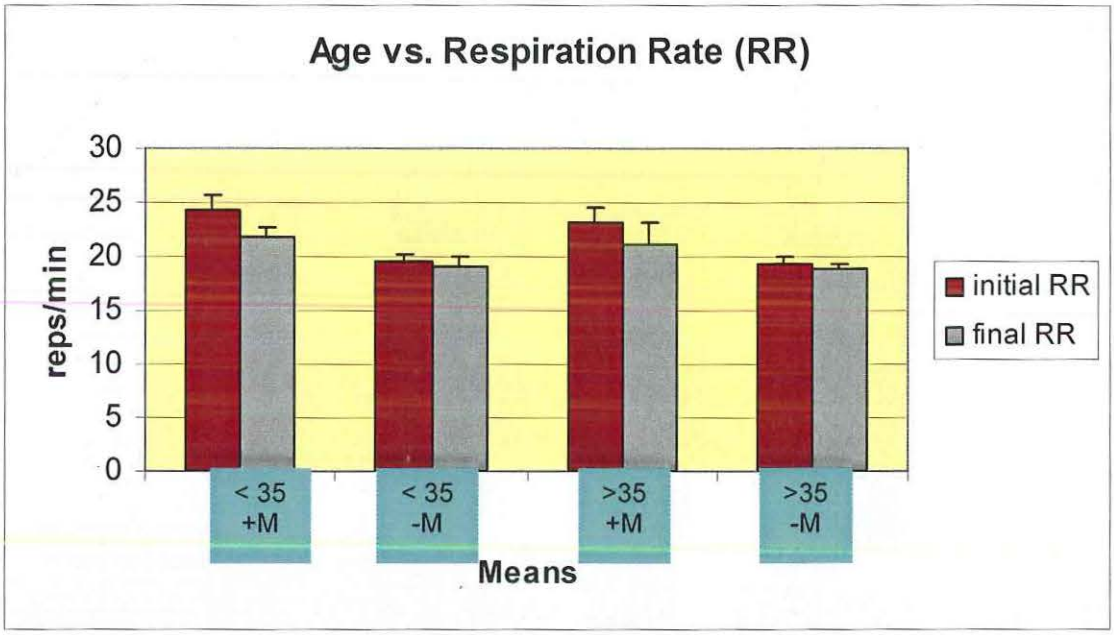


Figure 17. Means of Respiration Rate for age categories

Table 18. Respiration Rate summary of means and ±SE for age categories

Age vs. Respiration Rate (RR)	a) Initial RR Reading +M & -M	b) Difference between Initial & Final RR reading +M	c) Difference between Initial & Final RR reading -M	d) Final RR Reading +M & -M	e) Statistical Difference between b) & c)
<35 yrs n=40	+M =24.4 SE ±1.40 -M =19.5 SE ±0.758 Mean difference 4.86 ±1.59 **p = 0.005** yes significant	I = 24.4 SE ± 1.40 F = 21.8 SE ±1.00 Mean decrease 2.6 ±1.27 **p = 0.052** no significance	I = 19.5 SE ± 0.758 F = 19.2 SE ±0.768 Mean decrease 0.352 ±0.308 **p = 0.269** no significance	+M =21.7 SE ±1.00 -M =19.2 SE ±0.768 Mean difference 2.61 ±1.27 **p = 0.047** yes significant	**p = 0.671** no significance
>35 yrs n=54	+M =23 SE ±1.49 -M =19.3 SE ±0.616 Mean difference 3.75 ±1.61 **p =0.027** yes significant	I = 23.1 SE ± 1.49 F = 21.1 SE ±2.16 Mean decrease 1.95 ±1.34 **p = 0.158** no significance	I = 19.3 SE ± 0.616 F = 18.9 SE ±0.522 Mean decrease 0.466 ±0.207 **p = 0.032** yes significance	+M =21.1 SE ±2.16 -M =18.8 SE ±0.522 Mean difference 2.26 ±2.22 **p = 0.320** no significance	**p = 0.177** no significance

+M = midazolam
-M = no midazolam
I = initial reading
F = final reading
$\bar{x}$ = mean
p = significance value
SE± = Standard error mean

4.3.4. Statistical analysis of age vs. pulse rate

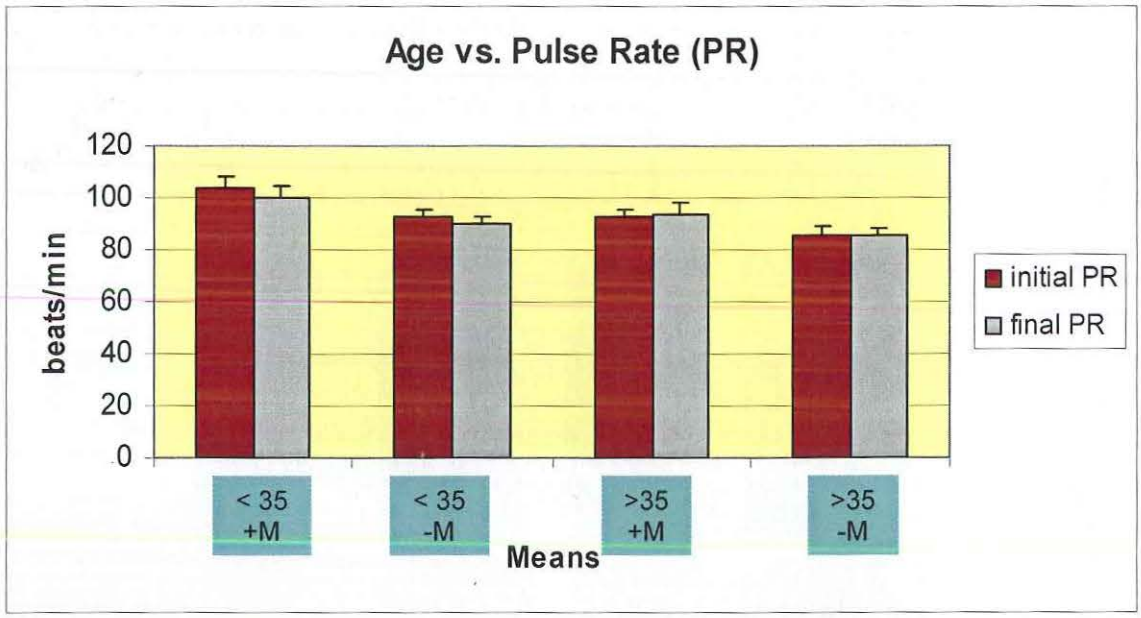


Figure 18. Means of Pulse Rate for age categories

Table 19. Pulse Rate summary of means and ±SE for age categories

Age vs. Pulse Rate (PR)	a) Initial PR Reading +M & -M	b) Difference between Initial & Final PR reading +M	c) Difference between Initial & Final PR reading -M	d) Final PR Reading +M & -M	e) Statistical Difference between b) & c)
<35 yrs n=40	+M =103.3 SE ±4.62 -M =92.3 SE ±2.97 Mean difference 10.9 ±5.5 **p = 0.054** no significance	I = 103.3 SE ± 4.62 F = 29.6 SE ±4.67 Mean decrease 3.65 ±1.72 **p = 0.045** yes significant	I = 92.3 SE ± 2.97 F = 89.6 SE ±3.30 Mean decrease 2.64 ±1.16 **p = 0.037** yes significant	+M =99.6 SE ±4.67 -M =89.6 SE ±3.30 Mean difference 9.96 ±5.7 **p = 0.090** no significance	**p = 0.814** no significance
>35 yrs n=54	+M =92.7 SE ±3.01 -M =85.7 SE ±3.02 Mean difference 7.05 ±4.32 **p = 0.109** no significance	I = 92.7 SE ± 3.01 F = 93.9 SE ±4.54 Mean decrease 1.16 ±2.83 **p = 0.684** no significance	I = 85.7 SE ± 3.03 F = 85.4 SE ±2.84 Mean decrease 0.266 ±1.07 **p = 0.806** no significance	+M =93.9 SE ±4.54 -M =85.4 SE ±2.84 Mean difference 8.48 ±5.15 **p = 0.106** no significance	**p = 0.623** no significance

+M = midazolam
-M = no midazolam
I = initial reading
F = final reading
p = significance value
SE± = Standard error mean

4.4. Analysis of Head Injury & Midazolam/Non-midazolam

4.4.1. Statistical analysis of head injury vs. systolic blood pressure

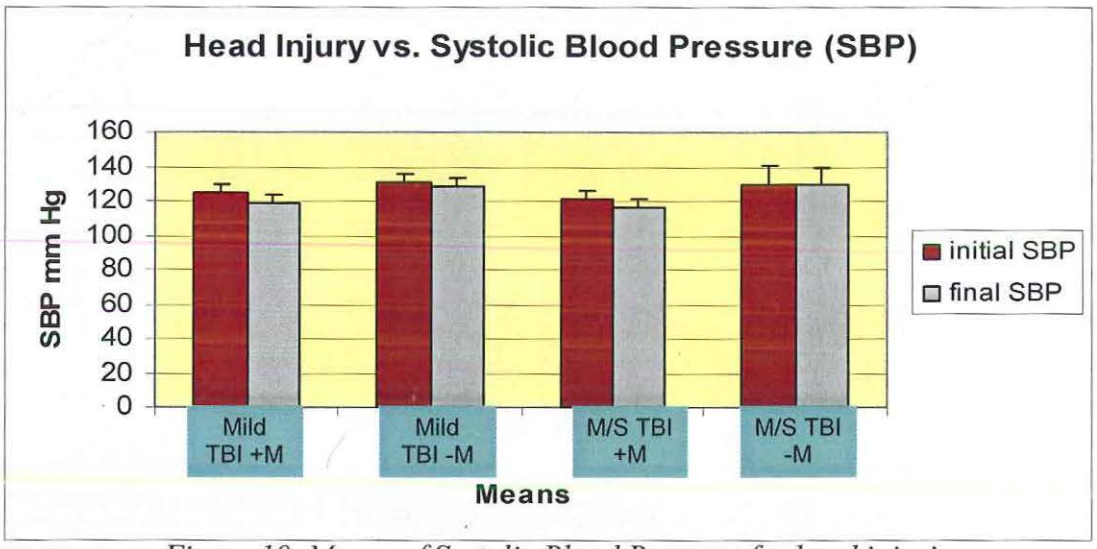


Figure 19. Means of Systolic Blood Pressure for head injuries

Table 20. Systolic Blood Pressure summary of means and ±SE for head injuries

Head Injury vs. Systolic Blood Pressure (SBP)	a) Initial SBP Reading +M & -M	b) Difference between Initial & Final SBP reading +M	c) Difference between Initial & Final SBP reading -M	d) Final SBP Reading +M & -M	e) Statistical Difference between b) & c)
MILD TBI n=56	+M =125.2 SE ±5.14 -M =131 SE ±4.86 Mean difference 5.98 ±7.73 **p = 0.443** no significance	I = 125.2 SE ± 5.14 F = 118.9 SE ±4.91 Mean decrease 6.21 ±3.45 **p = 0.089** no significance	I = 131.1 SE ± 4.86 F = 128.5 SE ±4.39 Mean decrease 2.67 ±1.01 **p = 0.012** yes significant	+M =118.9 SE ±4.91 -M =128.5 SE ±4.39 Mean difference 9.5 ±7.07 **p = 0.185** no significance	**p = 0.099** no significance
MODERATE/ SEVERE TBI n=40	+M =121.4 SE ±4.55 -M =130 SE ±10.7 Mean difference 8.57 ±9.96 **p = 0.395** no significance	I = 121.4 SE ± 4.54 F = 116.4 SE ±4.9 Mean decrease 5 ±3.37 **p = 0.148** no significance	I = 130 SE ± 10.7 F = 129.6 SE ±9.41 Mean decrease 0.4 ±0.259 **p = 0.801** no significance	+M =116.4 SE ±4.91 -M =129.6 SE ±9.41 Mean difference 13.2 ±10.1 **p = 0.199** no significance	**p = 0.308** no significance

+M = midazolam
-M = no midazolam
I = initial reading
F = final reading
p = significance value
SE± = Standard error mean
Mild TBI = mild traumatic brain injury
M/S TBI = moderate/severe traumatic brain injury

4.4.2. Statistical analysis of head injury vs. oxygen saturation

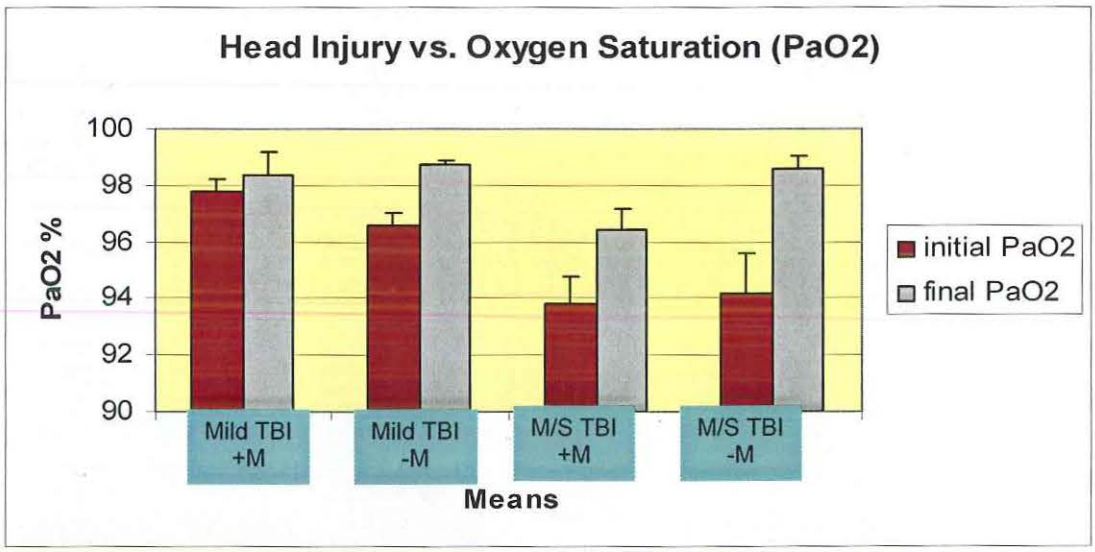


Figure 20. Means of Oxygen Saturation for head injuries

Table 21. Oxygen Saturation summary of means and ±SE for head injuries

Head Injury vs. Oxygen Saturation (PaO2)	a) Initial PaO2 Reading +M & -M	b) Difference between Initial & Final PaO2 reading +M	c) Difference between Initial & Final PaO2 reading -M	d) Final PaO2 Reading +M & -M	e) Statistical Difference between b) & c)
MILD TBI n=56	+M =95.8 SE ±0.394 -M =96.5 SE ±0.469 Mean difference 1.25 ±0.433 **p = 0.047** yes significance	I = 97.8 SE ± 0.394 F = 98.4 SE ±0.773 Mean increase 0.579 ±0.863 **p = 0.511** not significant	I = 96.5 SE ± 0..469 F = 98.7 SE ±0.176 Mean increase 2.19 ±0.447 **p = 0.000** yes significant	+M =98.3 SE ±0.773 -M =98.7 SE ±0.176 Mean difference 0.361 ±0.602 **p = 0.551** no significance	**p = 0.432** no significance
MODERATE/ SEVERE TBI n=40	+M =93.7 SE ±0.979 -M =94.2 SE ±1.36 Mean difference 1.25 ±0.433 **p = 0.818** no significance	I = 93.8 SE ± 0.978 F = 96.4 SE ±0.713 Mean increase 2.66 ±0.501 **p = 0.000** yes significant	I = 94.2 SE ± 1.36 F = 98.6 SE ±0.400 Mean increase 4.4 ±1.15 **p = 0.004** yes significant	+M =96.4 SE ±0.714 -M =98.6 SE ±0.40 Mean difference 2.17 ±1.28 **p = 0.095** no significance	**p = 0.012** yes significant

+M = midazolam
-M = no midazolam
I = initial reading
F = final reading
p = significance value
SE± = Standard error mean
Mild TBI = mild traumatic brain injury
M/S TBI = moderate/severe traumatic brain injury

4.4.3. Statistical analysis of head injury vs. respiration rate

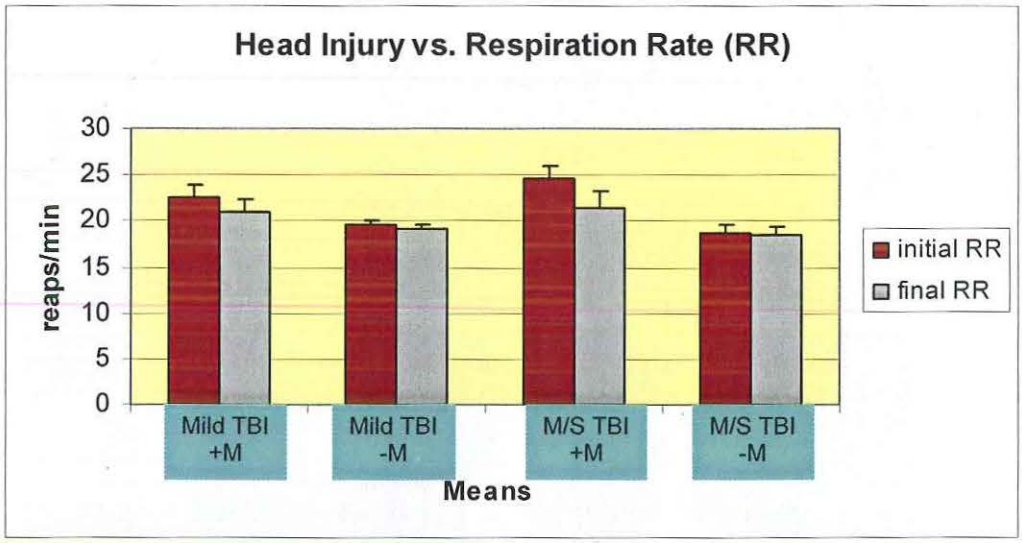


Figure 21. Means of Respiration Rate for head injuries

Table 22. Respiration Rate summary of means and ±SE for head injuries

Head Injury vs. Respiration Rate (RR)	a) Initial RR Reading +M & -M	b) Difference between Initial & Final RR reading +M	c) Difference between Initial & Final RR reading -M	d) Final RR Reading +M & -M	e) Statistical Difference between b) & c)
MILD TBI n=56	+M =22.6 SE ±1.31 -M =19.6 SE ±0.570 Mean difference 3.01 ±1.43 **p = 0.046** yes significant	I = 22.6 SE ± 1.31 F = 20.9 SE ±1.39 Mean decrease 1.63 ±0.922 **p = 0.094** no significance	I = 19.5 SE ± 0.570 F = 19 SE ±0.506 Mean decrease 0.486 ±0.211 **p = 0.027** yes significant	+M =20.9 SE ±1.39 -M =19 SE ±0.505 Mean difference 1.86 ±1.48 **p = 0.221** no significance	**p = 0.412** no significance
MODERATE/ SEVERE TBI n=40	+M =24.6 SE ±1.39 -M =18.8 SE ±0.742 Mean difference 5.8 ±1.58 **p = 0.001** yes significant	I = 24.6 SE ± 1.39 F = 21.5 SE ±1.68 Mean decrease 3.1 ±1.41 **p = 0.035** yes significant	I = 18.8 SE ± 0.742 F = 18.6 SE ±0.791 Mean decrease 0.20 ±0.20 **p = 0.343** no significance	+M =21.5 SE ±1.68 -M =18.6 SE ±0.792 Mean difference 2.93 ±2.97 **p = 0.330** no significance	**p = 0.611** no significance

+M = midazolam
-M = no midazolam
I = initial reading
F = final reading
p = significance value
SE± = Standard error mean
Mild TBI = mild traumatic brain injury
M/S TBI = moderate/severe traumatic brain injury

4.4.4. Statistical analysis of head injury vs. pulse rate

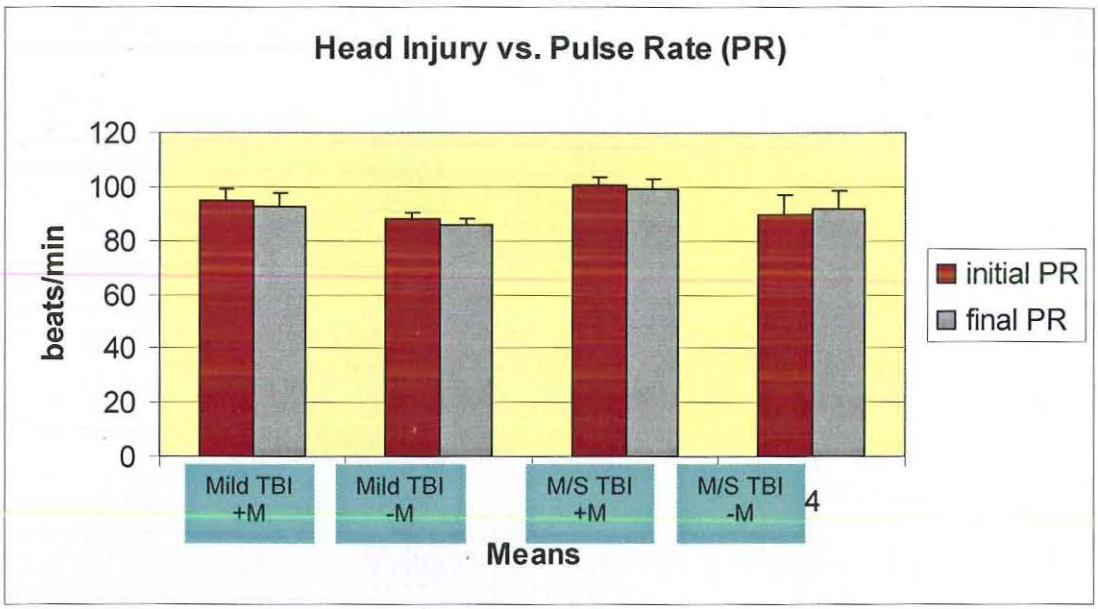


Figure 22. Means of Pulse Rate for head injuries

Table 23. Pulse Rate summary of means and ±SE for head injuries

Head Injury vs. Pulse Rate (PR)	a) Initial PR Reading +M & -M	b) Difference between Initial & Final PR reading +M	c) Difference between Initial & Final PR reading -M	d) Final PR Reading +M & -M	e) Statistical Difference between b) & c)
MILD TBI n=56	+M =94.7 SE ±4.55 -M =87.7 SE ±2.14 Mean difference 6.98 ±5.02 **p = 0.177** no significance	I = 94.7 SE ± 4.54 F = 92.7 SE ±5.12 Mean decrease 2.0 ±1.5 **p = 0.200** no significance	I = 87.7 SE ± 2.14 F = 85.7 SE ±2.07 Mean decrease 1.94 ±0.909 **p = 0.039** yes significant	+M =92.6 SE ±5.12 -M =85.7 SE ±2.07 Mean difference 6.92 ±5.52 **p = 0.222** no significance	**p = 0.978** no significance
MODERATE/ SEVERE TBI n=40	+M =100.3 SE ±3.44 -M =89.5 SE ±7.22 Mean difference 10.8 ±7.25 **p = 0.144** no significance	I = 100.3 SE ± 3.44 F = 98.6 SE ±3.94 Mean decrease 1.46 ±0.546 **p = 0.589** no significance	I = 89.5 SE ± 7.22 F = 91.4 SE ±6.84 Mean decrease 1.9 ±1.55 **p = 0.252** no significance	+M =98.8 SE ±3.94 -M =91.4 SE ±6.84 Mean difference 7.46 ±7.88 **p = 0.349** no significance	**p = 0.684** no significance

+M = midazolam
-M = no midazolam
I = initial reading
F = final reading
p = significance value
SE± = Standard error mean
Mild TBI = mild traumatic brain injury
M/S TBI = moderate/severe traumatic brain injury

4.5. Mild TBI Results

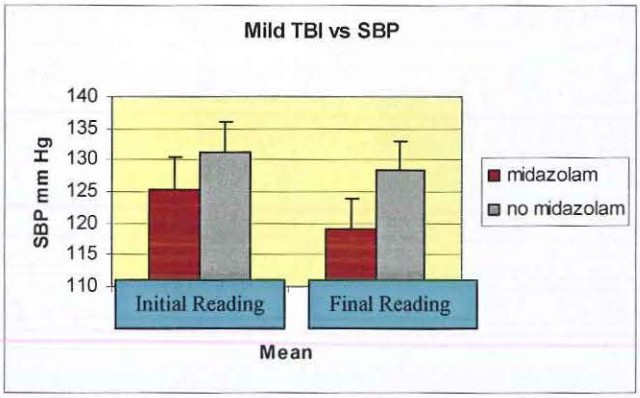


Figure 23. Means of Systolic Blood Pressure for Mild TBI

Table 24. Systolic Blood Pressure summary of means and ±SE for Mild TBI

	Initial vs. Final SBP Midazolam (n= 19)	Initial vs. Final SBP no midazolam (n= 37)	Initial SBP reading +M & -M	Final SBP reading +M & -M	Statistical difference between the differences for +M & -M
Mild TBI vs. SBP	I =125.2 SE ±5.14 F =118.9 SE ±4.91 **p = 0.044** yes significant	I =131.1 SE ±4.86 F =128.5 SE ±4.39 **p = 0.006** yes significant	I =129.1 SE ±3.64 **p = 0.201** no significance	F =125.2 SE ±3.38 **p = 0.078** no significance	Mean difference 3.87 ±1.35 **p = 0.168** no significance

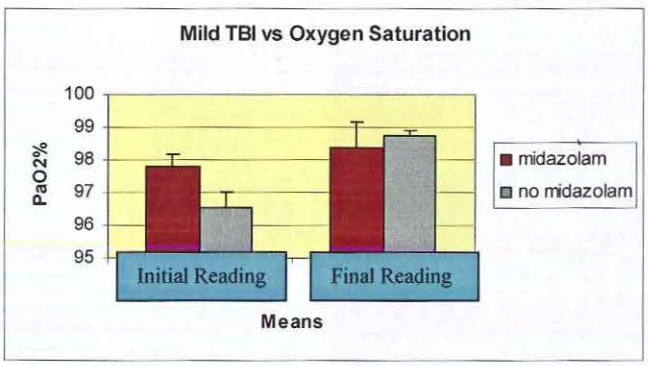


Figure 24. Means of Oxygen Saturation for Mild TBI

Table 25. Oxygen Saturation summary of means and ±SE for Mild TBI

	Initial vs. Final PaO_2 midazolam (n= 19)	Initial vs. Final PaO_2 no midazolam (n= 37)	Initial PaO_2 reading +M & -M	Final PaO_2 reading +M & -M	Statistical difference between the differences for +M & -M
Mild TBI vs. PaO_2	I =97.8 SE ±0.394 F =98.4 SE ±0.773 **p = 0.255** no significance	I =96.5 SE ±0.469 F =98.7 SE ±0.176 **p = 0.000** yes significant	I =96.9 SE ±0.345 **p = 0.023** yes significant	F =98.6 SE ±0.283 **p = 0.327** no significance	Mean difference 1.64 ±0.423 **p = 0.054** no significance

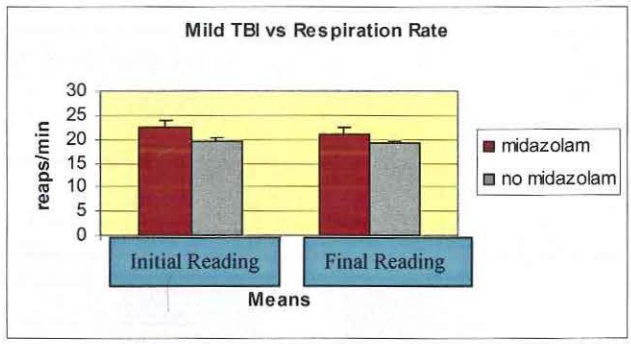


Figure 25. Means of Respiration Rate for Mild TBI

Table 26. Respiration Rate summary of means and ±SE for Mild TBI

	Initial vs. Final RR Midazolam (n= 19)	Initial vs. Final RR no midazolam (n= 37)	Initial RR reading +M & -M	Final RR reading +M & -M	Statistical difference between the differences for +M & -M
Mild TBI vs. RR	I =22.6 SE ±1.31 F =20.9 SE ±1.39 **p = 0.047** yes significant	I =19.6 SE ±0.570 F =19 SE ±0.505 **p = 0.013** yes significant	I =20.6 SE ±0.608 **p = 0.023** yes significant	F =19.7 SE ±0.583 **p = 0.110** no significance	Mean difference 0.875 ±0.344 **p = 0.119** no significance

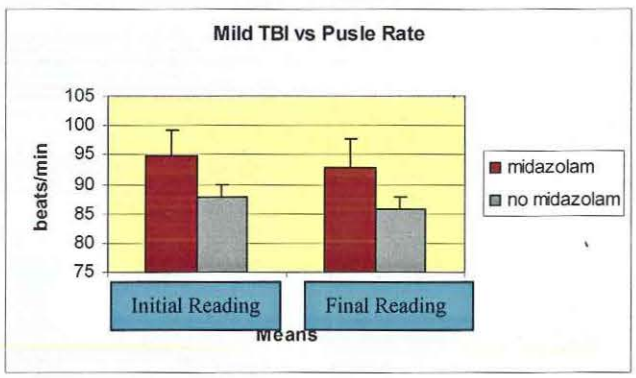


Figure 26. Means of Pulse Rate for Mild TBI

Table 27. Pulse Rate summary of means and ±SE for Mild TBI

	Initial vs. Final PR midazolam (n= 19)	Initial vs. Final PR no midazolam (n= 37)	Initial PR reading +M & -M	Final PR reading +M & -M	Statistical difference between the differences for +M & -M
Mild TBI vs. PR	I =94.7 SE ±4.55 F =92.7 SE ±5.12 **p = 0.100** no significance	I =87.7 SE ±2.14 F =85.7 SE ±2.07 **p = 0.013** yes significant	I =20.6 SE ±0.608 **p = 0.088** no significance	F =19.7 SE ±0.583 **p = 0.111** no significance	Mean difference 1.96 ±0.780 **p = 0.488** no significance

4.6. Moderate TBI Results

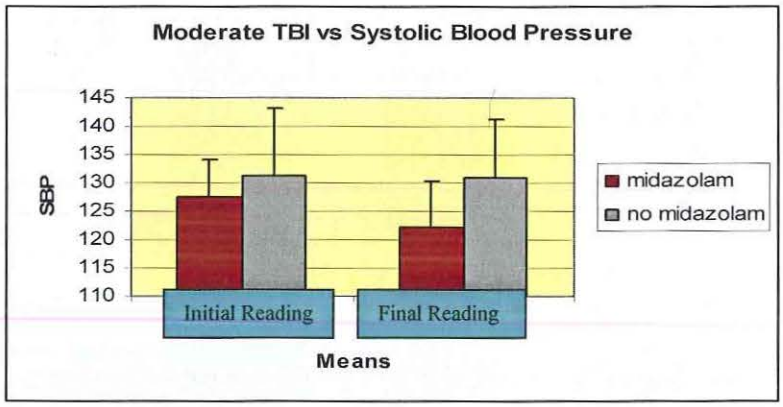


Figure 27. Means of Systolic Blood Pressure for Moderate TBI

Table 28. Systolic Blood Pressure summary of means and ±SE for Mod. TBI

	Initial vs. Final SBP midazolam (n= 16)	Initial vs. Final SBP no midazolam (n= 9)	Initial SBP reading +M & -M	Final SBP reading +M & -M	Statistical difference between the differences for +M & -M
Moderate TBI vs. SBP	I =127.4 SE ±6.69 F =122.2 SE ±8.05 **p = 0.183** no significance	I =131.1 SE ±11.8 F =130.8 SE ±10.4 **p = 0.450** no significance	I =128.7 SE ±5.92 **p = 0.394** no significance	F =125.3 SE ±6.29 **p = 0.258** no significance	Mean difference -3.4 ±3.6 **p = 0.202** no significance

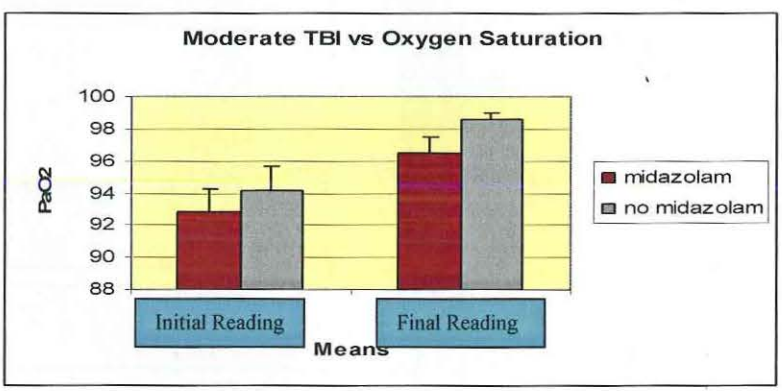


Figure 28. Means of Oxygen Saturation for Moderate TBI

Table 29. Oxygen Saturation summary of means and ±SE for Moderate TBI

	Initial vs. Final PaO_2 midazolam (n= 16)	Initial vs. Final PaO_2 no midazolam (n= 9)	Initial PaO_2 reading +M & -M	Final PaO_2 reading +M & -M	Statistical difference between the differences for +M & -M
Moderate TBI vs. PaO_2	I =92.8 SE ±1.46 F =96.4 SE ±1.03 **p = 0.000** yes significant	I =94.1 SE ±1.51 F =98.5 SE ±0.444 **p = 0.004** yes significant	I =93.3 SE ±1.07 **p = 0.272** no significance	F =97.2 SE ±0.702 **p = 0.037** yes significant	Mean difference 3.92 ±0.658 **p = 0.296** no significance

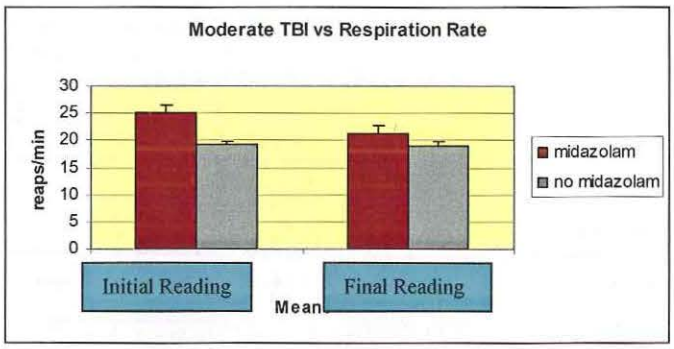


Figure 29. Means of Respiration Rate for Moderate TBI

Table 30. Respiration Rate summary of means and ±SE for Moderate TBI

	Initial vs. Final RR midazolam (n= 16)	Initial vs. Final RR no midazolam (n= 9)	Initial RR reading +M & -M	Final RR reading +M & -M	Statistical difference between the differences for +M & -M
Moderate TBI vs. RR	I =24.9 SE ±1.7 F =21.2 SE ±1.43 **p = 0.028** yes significant	I =19.1 SE ±1.7 F =18.8 SE ±1.43 **p = 0.173** no significance	I =22.8 SE ±1.24 **p = 0.003** yes significant	F =20.3 SE ±0.978 **p = 0.089** no significance	Mean difference 2.48 ±1.19 **p = 0.035** yes significant

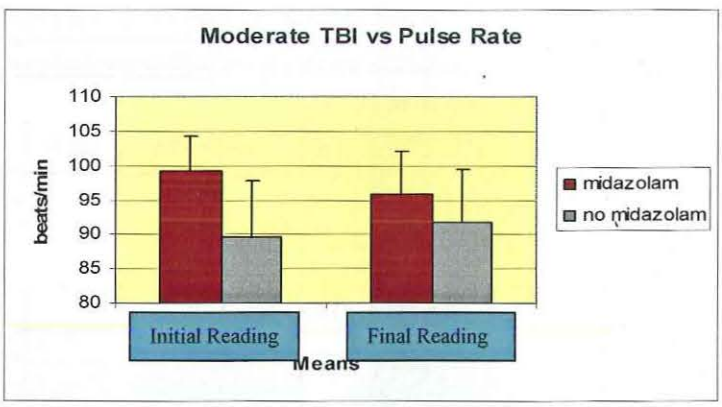


Figure 30. Means of Pulse Rate for Moderate TBI

Table 31. Pulse Rate summary of means and ±SE for Moderate TBI

	Initial vs. Final PR Midazolam (n= 16)	Initial vs. Final PR no midazolam (n= 9)	Initial PR reading +M & -M	Final PR reading +M & -M	Statistical difference between the differences for +M & -M
Moderate TBI vs. PR	I =99.2 SE ±4.97 F =95.7 SE ±6.31 **p = 0.219** no significance	I =89.6 SE ±8.07 F =91.7 SE ±7.63 **p = 0.127** no significance	I =95.8 SE ±4.31 **p = 0.165** no significance	F =94.3 SE ±4.80 **p = 0.346** no significance	Mean difference 1.48 ±2.88 **p = 0.124** no significance

4.7. Severe TBI Results

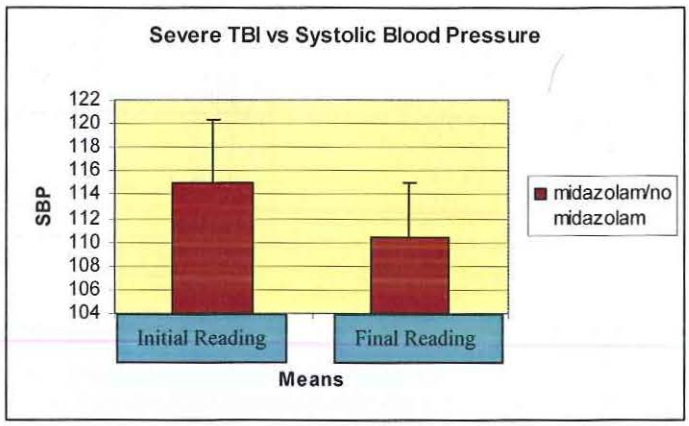


Figure 31. Means of Systolic Blood Pressure for Severe TBI

Table 32. Systolic Blood Pressure summary of means and ±SE for Severe TBI

Midazolam (n=14) No midazolam (n=1)	Initial SBP	Final SBP	Statistical difference between Initial vs. Final SBP
Severe TBI vs. SBP	mean = 115 SE = ± 5.36	mean = 110 SE = ± 4.53	**p = 0.098** no significance

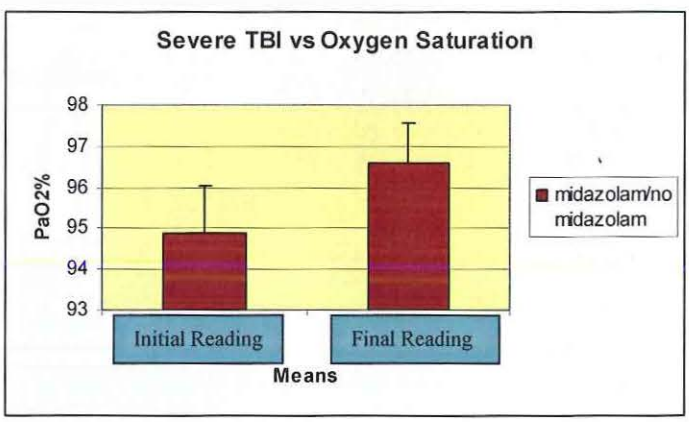


Figure 32. Means of Oxygen Saturation for Severe TBI

Table 33. Oxygen Saturation summary of means and ±SE for Severe TBI

Midazolam (n=14) No midazolam (n=1)	Initial PaO_2	Final PaO_2	Statistical difference between Initial vs. Final PaO_2
Severe TBI vs. PaO_2	mean = 94.8 SE = ± 1.16	mean = 96.6 SE = ± 0.960	**p = 0.002** yes significant

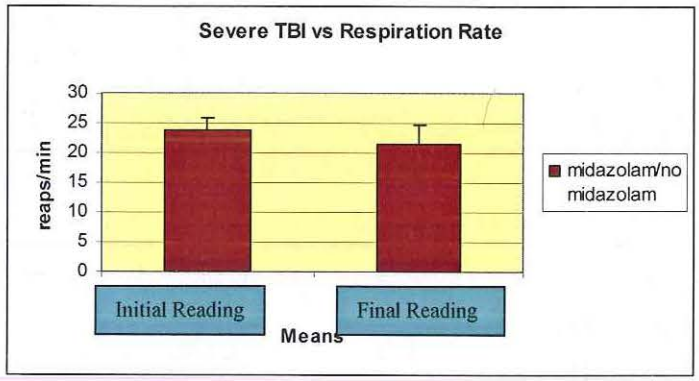


Figure 33. Means of Respiration Rate for Severe TBI

Table 34. Respiration Rate summary of means and ±SE for Severe TBI

Midazolam (n=14) No midazolam (n=1)	Initial RR	Final RR	Statistical difference between Initial vs. Final RR
Severe TBI vs. RR	mean = 23.7 SE = ± 2.25	mean = 21.5 SE = ± 3.08	**p = 0.156** no significance

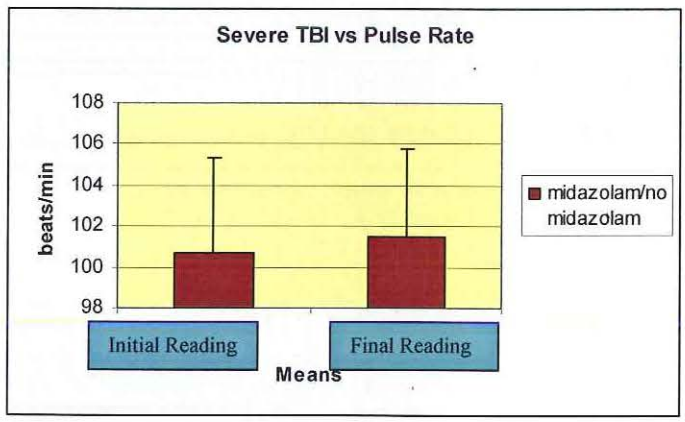


Figure 34. Means of Pulse Rate for Severe TBI

Table 35. Pulse Rate summary of means and ±SE for Severe TBI

Midazolam (n=14) No midazolam (n=1)	Initial RR	Final RR	Statistical difference between Initial vs. Final RR
Severe TBI vs. RR	mean = 100.6 SE = ± 4.62	mean = 101 SE = ± 4.25	**p = 0.385** no significance

5. Discussion

Midazolam/Non midazolam analysis

The analysis of the systolic blood pressure (SBP) in relation to midazolam and non-midazolam cohorts showed a statistical significance between initial and final readings for each cohort (see table 9). The lower initial SBP readings for the midazolam cohort may be a consequence of the multiple injuries sustained by the patients. Such injuries to the head imply greater blood loss, therefore resulting in lower initial SBP readings [85]. The mean decrease for the midazolam cohort was greater than 5 mmHg which was not considered clinically significant as patients were not in danger of reaching a hypotensive state [72]. There was also a significant difference between the final readings comparing both midazolam and non-midazolam cohorts. The final reading for the midazolam was not as high as the non-midazolam cohort (see table 9). However the mean final reading was considered safe and was not indicative of hypotension.

A statistical significance was also noted between the initial and final readings for oxygen saturation in the midazolam and non-midazolam cohorts (see table 10). It is important to note that all patients in this study received oxygen supplementation during treatment. This explains the increase in final oxygen saturation readings for both the midazolam and non-midazolam cohorts. There is a statistical significance between the final PaO_2 reading between midazolam and non-midazolam cohorts. Midazolam's final PaO_2 readings increased to 97% compared to a 99% PaO_2 increase for the non-midazolam cohort. Again this may be due to the severity of injuries sustained by the midazolam study population.

The analysis of respiration and pulse rate in relation to midazolam and non-midazolam cohorts revealed a significant difference between initial respiration and pulse rate reading for the midazolam cohort (tables 11 & 12). Patients treated with midazolam expressed higher initial respiration and pulse rate readings compared to non-midazolam patients. This may be due to the fact that patients treated with midazolam displayed uncontrollable or aggressive behaviours which directly correlate to increased physiological breathing and heart rate patterns. Although there was a noted statistical difference between initial respiration and pulse rate readings for the midazolam cohort this was of no clinical significance.

Gender category

In relation to the comparison of initial and final readings, midazolam and non-midazolam groups for males, it was interesting to note that there was a significant drop in SBP (see table 13, figure 10). This translates to a significant drop in oxygen saturation when comparing these same groups; however this is not of clinical importance and probably relates to the nature of the injuries of the group. It must be borne in mind that the patients selected to receive midazolam were not randomly selected, but were allocated the drug on the basis of their antisocial or uncontrollable behaviour. This could account for the differences noted between initial readings of both midazolam and non-midazolam group in respect of pulse and respiration rate. Differences between the initial readings of these groups in respect of oxygen saturation and blood pressure were also noted, but were not of statistical significance.

The analysis of oxygen saturation on the basis of gender revealed no significant differences between initial and final readings, in those patients given midazolam relative to those patients who did not receive midazolam for either the males or females. Yet the males displayed a significant drop in final reading under the influence of midazolam (see table 14). Discounting physiological differences, this reflects the seriousness of the injuries of the male cohort, especially in relation to head injuries, which mainly arose as a consequence of motor vehicle accidents. The majority of males in this study were aged between 25 to 35 years and were involved in motor vehicle accidents, while the majority of females were aged 66 years and older and sustained head injuries due to falls and direct trauma to the head. This natural bias in the data could not be overcome due to the limitations of complete patient care records.

Age category

The age vs. Systolic Blood Pressure category did not present statistical significance for the less than 35 year olds. In this category, patients treated with midazolam recorded 14.3 mm Hg less than those not treated with midazolam. The under thirty fives showed a 6.2 mm Hg mean decrease for the midazolam patients compared to a 2.8 mm Hg in the non-midazolam group (see table 17).

A statistical significance was noted in all but three variables in relation to age vs. oxygen saturation. Patients 35 years and older recorded similar mean oxygen saturation

readings (see table 18) in the midazolam and non-midazolam cohorts, prior to any form of treatment (this also excludes oxygen supplementation). Patients over 35 years in both the midazolam and non-midazolam cohorts shared a 1.6 % oxygen saturation difference after treatment. The patients over 35 year's displayed a statistical significance between those treated with midazolam compared to those not treated with midazolam. The mean PaO_2 increase of 3.6 % in the non-midazolam patients, compared to a 2.2 % increase with the midazolam treated patients, suggests a greater PaO_2 increase in patients not treated with midazolam. Although there is statistical significance between the midazolam and non-midazolam patients the increase in oxygen saturation is not clinically significant [61, 62]. Oxygen supplementation was administered during both the first and second readings.

All variables recorded for the less than 35 year olds displayed statistical significance when analysed for age vs. oxygen saturation. It appears the mean increase in oxygen saturation is greater in the older than 35 year olds than the less the 35 year olds. It is important to remember that although there is a statistical difference with oxygen saturation between those treated with midazolam it does not suggest symptoms of hypoxia in the patients.

Head Injury - Mild vs. Mod/Severe

A statistical difference was noted in the analysis of moderate/severe (m/s) head injury and oxygen saturation. The final reading for the m/s midazolam cohort reached an average 96% PaO_2, after receiving oxygen ventilation while, in the non midazolam m/s head injury cohort, final PaO_2 readings averaged 99%. This may suggest hypoxic activities and it may not necessarily be the nature of the head injury. However, when the m/s head injury midazolam cohort was separately divided into moderate vs. severe head injury, analysis demonstrated a clear statistical difference between severe head injuries vs. oxygen saturation and no statistical significance between moderate head injuries vs. oxygen saturation. This would suggest that midazolam does not engender hypoxic activities and in fact it is the severity of the head injury that influences hypoxia. A significant difference between initial and final midazolam and initial and final non-midazolam respiration rate suggests that patient's agitated behaviour increases breathing patterns resulting in patients receiving midazolam for calming purposes. There was no statistical significance between head injuries and systolic blood pressure and pulse rate.

The objective of this study was to evaluate the effect midazolam had on head injured patients in the prehospital setting. The study aimed to determine whether midazolam increased symptoms of hypotension and hypoxia in patients with head injuries.
It has been shown that the patients/cases who received midazolam displayed decreased SBP readings, lowered respiration rates and a greater decrease in pulse rate compared to patients cases who did not receive midazolam for sedation. Although overall symptoms of hypotension were evident in patients/cases that received midazolam, levels were not clinically significant. Oxygen saturation appears to be significant in most cases analysed. Clear distinctions between the midazolam and non-midazolam cohorts suggest midazolam does in fact affect levels of oxygen within head injured patients. However, the oxygen saturation readings are not low enough to be considered clinically significant [85].

Only three cases showed SBP readings lower than 90 mm Hg after midazolam administration. No patients experienced clinical symptoms of respiratory depression. The lowest recorded PaO_2 reading was 82% for a female aged over 65.

Head Injuries- mild, moderate and severe

Mild Head Injuries

Both the midazolam and non-midazolam cohorts showed an average decrease in systolic blood pressure (see table 25). This may suggest that all patients who had sustained mild head injuries displayed similar physiological decreases in systolic blood pressure. It appears midazolam did not cause symptoms of hypotension as patients not treated with midazolam exhibited the same decrease in systolic blood pressure.

Non-midazolam patients did show a statistically significant difference in oxygen saturation relative to the treated patients. It is interesting that the non-midazolam patients' initial PaO_2 readings were slightly lower than the initial PaO_2 readings of midazolam patients. However overall none of the variables measured suggests that midazolam caused hypoxic levels.

Statistical significance in respiration rate appears to affect both the midazolam and non-midazolam patients equally. Although those patients in the mild head injuries plus

midazolam cohort displayed a higher initial respiration rate than the mild head injuries no-midazolam cohort the greater decrease in breathing rate after administration of midazolam showed this to be of no clinical significance.

Patients treated with midazolam displayed higher initial and final pulse rate reading than the non-midazolam cohort. This could be due the fact that the patients treated with midazolam are a select group displaying uncontrollable or aggressive behaviours. When comparing pulse rate between midazolam and non-midazolam cohorts, a larger drop in pulse rate was noted with the non-midazolam cohort.

Moderate Head injury

A statistically significant increase in oxygen saturation was recorded for both midazolam and non-midazolam patients. Statistical significance was also noted for the mean final oxygen saturation reading (see table 30) between the midazolam and non-midazolam patients; it does not reach 98%. It is important that oxygen saturation readings reach 98% during head trauma. However, patients treated during this study all received oxygen supplementation and oxygen saturation readings were carefully maintained and monitored. A 98% oxygen saturation reading does not indicate hypoxia and is of no detrimental effect to patients[46]. One of the problems in interpreting the data is the uncertainty of what pharmaceuticals (or other drugs) the patients have in their systems, and whether the administration of midazolam will displace these agents from the transport proteins in the bloodstream, producing multifactorial effects.

The larger drop in breathing rate for the midazolam cohort compared to only a 1.7 resps per minute drop in the non-midazolam suggests midazolam patients displayed faster breathing patterns than the patients not treated with midazolam. Again this may be due to each patient treated with midazolam displaying aggressive or uncooperative behaviours therefore these patients' physiological responses were increased. Also, although the mean initial reading was higher in midazolam patients than non-midazolam patients (see table 31), all patients treated with midazolam did not display irregular breathing patterns. The overall drop in respiration rate did not reach clinical danger levels for individuals [90, 91].

No statistical significance was found with systolic blood pressure or pulse rate between midazolam treated patients and untreated patients. However the midazolam cohort displayed a lower systolic blood pressure (see table 28) for both the initial reading and final readings when compared to a much higher systolic reading for the non-midazolam cohort. This is unusual as patients receiving midazolam display aggressive characteristics that could influence increased symptoms of hypotension. However, this could be explained as patients treated with midazolam sustained a slightly higher GCS score, which suggests the more severe the head injury the greater the blood loss experienced by patients [85].

Severe Head Injuries

The mean drop in systolic blood pressure for the severely head injured patients is 5mm Hg. The initial SBP reading (see table 33) was not considered high and in fact it is within the normal healthy range. The drop in SBP is therefore not clinically significant to patients, as they were not hypotensive [85].

A statistical significance in the increase of oxygen saturation was noted. However the increase is not clinically significant even though the final oxygen saturation does not reach 97%. It is important to point out that the patients in the moderate head injury category have a mean of 97% oxygen saturation, the same as the severely head injured patients. The fact that the severely head injured patients and the moderate head injured patients had similar oxygen saturation levels validates combining these groups in the SPSS study. It is also supporting evidence that the level of oxygen administration during transportation to hospital is appropriate for each of these patient categories. It should be borne in mind that any potential effects of reducing oxygen saturation by midazolam could be counteracted by the administration of oxygen [59].

No clinical significance was noted with respiration rate or pulse rate in the severely head injured cohort. The severely head injured patients displayed slightly higher physiological symptoms of oxygen saturation and heart rate than the moderate head injured patients. Interestingly they displayed lower systolic blood pressure and breathing rate readings than the moderate head injuries. This may be due to swelling impinging on the cardiovascular medullary centres in the brain [85].

Comparing the analysis of the mild vs. moderate/severe head injuries in the Excel analyses showed no distinct difference between the two cohorts. Both these cohorts displayed statistically significant differences in oxygen saturation readings and a statistical significance found in systolic blood pressure, respiration rate or pulse rate in patients receiving midazolam relative to untreated patients. Also when comparing moderate vs. severe head injuries oxygen saturation variables stood out and both cohorts displayed statistical significance suggesting hypoxic activity is present in treated patients.

6. Conclusion

This study has demonstrated that midazolam is a safe and effective sedating agent used in the treatment of aggressive and uncontrollable patients who have sustained a head injury. The dosage of midazolam used on patients in this study varied from 5mg to 25mg. The patients who received 25mg of midazolam displayed similar physiological effects to those patients who only received 5mg of midazolam. Ultimately the varied dosage of midazolam used to treat aggressive head injured patients does not cause an increase in either hypotension or hypoxia.

It is interesting to speculate what would happen to oxygen saturation readings if no oxygen supplementation was administered to patients during treatment with midazolam? What would oxygen saturation levels be? It is our speculation that oxygen saturation levels would in fact remain fairly low if no oxygen supplementation was given to patients during midazolam use. Therefore hypoxia in patient's administered midazolam would be anticipated [59, 72].

Increases in respiration rate in patients treated with midazolam appear in the gender, age and head injury groups. Midazolam may be more active on the respiratory centres of the brain stem (pontine) than the cardiovascular medullary centres [46].

Ultimately this study found midazolam treatment did influence decrease in SBP, an increase in pulse rate and heart rate [91]along with lower oxygen saturation levels. However, in this study the variables are of no clinical significance [59, 92, 93] and do not suggest hypoxia or hypotension in patients. On the basis of this data and the analyses carried out, there were no demonstrable deleterious effects of midazolam on oxygen saturation or blood pressure in head injured patients. This is supporting evidence that this is a comparatively safe drug for use in the prehospital setting.

Bibliography

1. *Medication: Midazolam (Hypnovel).* Belmont: St John Ambulance WA Ambulance Service Inc.; 2004.
2. Galbraith A, Bullock S, Manias E. Antipsychotic Drugs. *Fundamental of Pharmacology.* 4th ed. Australia: Pearson: Prentice Hall; 2004.
3. W.A. SJA. HEAD TRAUMA: Clinical Practice Guidelines, September. St John Ambulance Australia W.A. Ambulance Service Inc; 2004:1-2.
4. Lahat E, Goldman M, Barr J, et al. Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: prospective randomised study. *British Medicine Journal.* 2000;321:83-86.
5. McGlone R, Smith M. Intranasal midazolam. An alternative in childhood seizures. *Emergency Medicine Journal.* 2001;18:232-234.
6. Huf G, Coutinho ESF, Adams CE. TREC-Rio trial: a randomised controlled trial for rapid tranquillisation for agitated patients in emergency psychiatric rooms. *Bio Med Central Psychiatry.* 2002;2:1-12.
7. Rainbow J, Browne GJ, Lam LT. Controlling seizures in the prehospital setting: Diazepam or midazolam? *Paediatric Child Health.* 18 Febuary 2002 2002;38:582-586.
8. TREC Collaborative Group. Rapid tranquillisation for agitated patients in emergency psychiatric rooms: a randomised trial of midazolam versus haloperidol plus promethazine. *Bio Med Journal.* 2003;327:1-6.
9. Harboard MG, Kyrkou NE, Kyrokou MR, et al. Use of intranasal midazolam to treat acute seizures in paediatric community settings. 7th April 2004 2004;40:556-558.
10. Shah I, Deshmukh CT. Intramuscular midazolam vs Intravenous diazepam for acute seizures. *Indian Journal of Pediatrics.* 2005;72:667-670.
11. Davis DP, Kimbro TA, Vike GM. The Use of Midazolam for Prehospital Rapid-Sequence Intubation May be associated with a Dose-related Increase in Hypotension. *Prehospital Emergency Care.* 2001;5(2):163-168.
12. Cooper, Bloom, Roth. The Complete Story of the Benzodiazepines. *The Biochemical Basis of Neuropharmacolgy.*: The Eaton T. Fores Research Centre.; 2002:1-20.
13. Dundee JW, Halliday NJ, Harper KW, et al. Midazolam: A review of its Pharmacological Properties and Therapeutic Use. *Drugs.* 1984;28:519-543.
14. Roche. Hypnovel® Midazolam. *Roche Products Pty Limite.* 2000.
15. Australia SJA. *Clinical Practice Guidelines 20.* Belmont: W.A. Ambulance Service Inc.; September 2004.
16. Australia SJA. *Clinical Practice Guidelines 33.* Perth, Belmont: W.A. Ambulance Service Inc.; June 2002.
17. Australia SJA. *Clinical Practice Guidelines-Medical Protocol 23.* Belmont: W.A. Ambulance Service Inc; July 1999.
18. *Head Trauma.* Belmont: St John Ambulance WA Ambulance Service Inc.; 2004.
19. Charney DS, Mihic SJ, Harris RA. *Hypnotics and Sedatives.* 10 ed: McGraw-Hill; 2001.
20. Roche. Hypnovel® Midazolam. *Roche Products Pty Limite.* Roche; 2004.
21. Australia M. *June 2005 MIMS Annual.* 29 ed. Australia: C & C Offset Printing Co., Ltd Hong Kong; 2005.

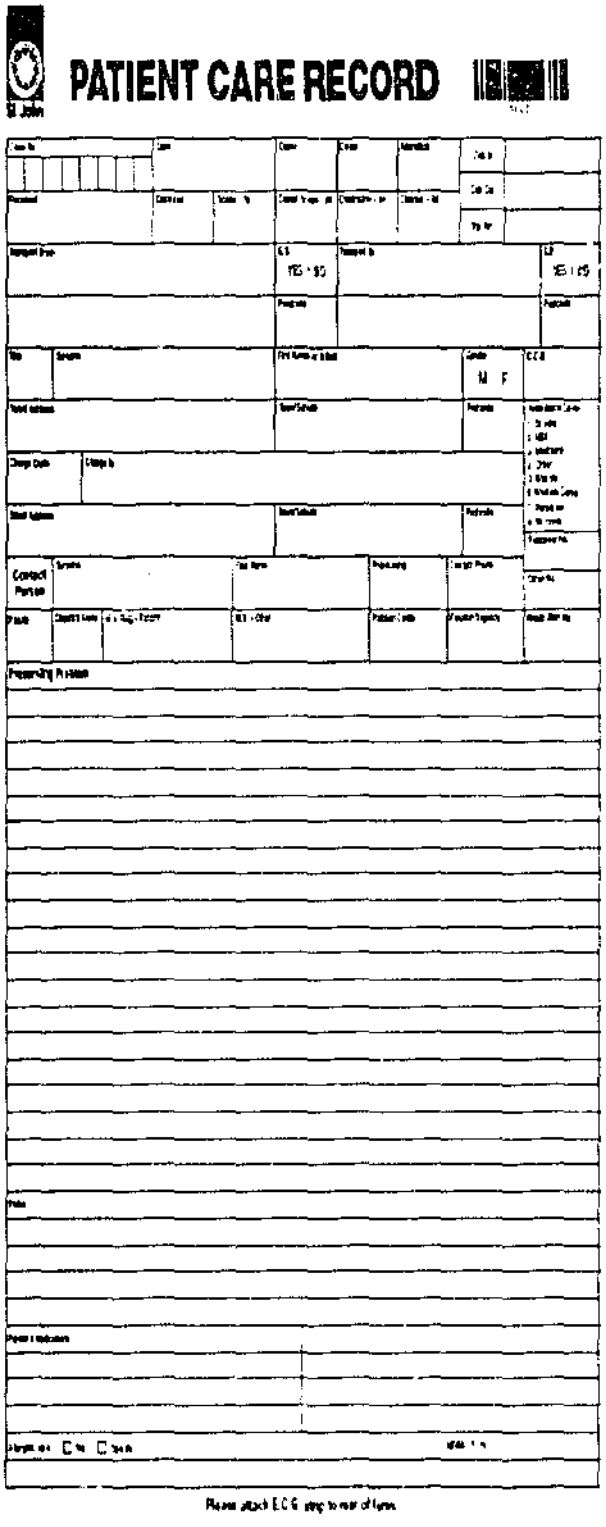
22. Australia M. Midazolam Injection.
23. Barnard EA, Skolnick P, Olsen W, et al. International Union of Pharmacology. XV. Subtypes of ?-Aminobutyric AcidA Receptors: Classification on the Basis of Subunit Structures and Receptor Function. *Pharmacological Reviews.* 1998;50(2):291-313.
24. Ping He, Court MH, Greenblatt DJ, et al. Genotype-phenotype associations of cytochrome P450 3A4 and 3A5 polymorphism with midazolam clearance in vivo. *Clinical Pharmacology and Therapeutics.* 2005;77(5):373-387.
25. Darlison MG, Pahal I, Thode C. Consequences of the Evolution of the GABAA Receptor Gene Family. *Cellular and Molecular Neurobiology.* 2005;25:607-624.
26. Herwaarden AE, Smit JW, Sparidans RW, et al. Midazolam and cyclosporine A metabolism in transgenic mice with liver-specific expression of human CYP3A4. *American Society for Pharmacology and Experimental Therapeutics.* 2005;4721:1-21.
27. Ping He, Court MH, Greenblatt DJ, et al. Genotype-phenotype associations of cytochrome P450 3A4 and 3A5 polymorphism with midazolam clearance in vivo. *Clinical Pharmacology and Therapeutics.* 2004;77(5):373-387.
28. W.A. SJA. Medication: Midazolam (Hypnovel), September. W.A. Ambulance Service Inc; 2004:1.
29. Mace SE, Barata IA, Cravero JP, et al. Clinical Policy: Evidence-Based Approach to Phamacologic Agents Used in Pediatric Sedation and Analgesia in the Emergency Department. *Annals of Emergency Medicine.* 2004;44(4):342-377.
30. Godwin SA, Caro DA, Wolf SJ, et al. Clinical Policy: Procedural Sedation and Analgesia in the Emergency Department. *Annals of Emergency Medicine.* 2005;45(2):177-196.
31. Knott JC, Taylor D, Castle DJ. Randomized Clinical Trial Comparing Intravenous Midazolam and Droperidol for Sedation of the Acutely Agitated Patient in Emergency Department. *Annals of Emergency Medicine.* 2005:1-7.
32. Weinbroum AA, Szold O, Ogorek D, et al. The midazolam-induced paradox phenomenon is reversible by flumazenil. Epidemiology, patient characteristics and review of the literature. *European Journal of Anaesthesiology.* 2001;18:789-797.
33. Thomas J. Midazolam Injection BP. *Australian Prescription Products Guide.* 2005;34(2):2269-2270
34. Unnerstall J, Kuhar M, Niehoff D, et al. Benzodiazepines receptors are coupled to a subpopulation of aminobutyric acid (GABA) receptors: evidence from a quantitatve autroradiographic study. . *Journal of Pharmacology and Expermental Therapeutics.* 1981;218:797-804.
35. Goodchild C, Serrao J. Intrathecal midazolam in the rat: evidence of spinally-mediated analgesia. *British Journal of Anaesthesia.* 1987;59:1563-1570.
36. Sawynok J. GABAergic mechanisms of analgesia: an update. *Pharmacology Biochemistry and Behavior.* 1987;26:463-474.
37. Kucken AM, Wagner DA, Ward PR, et al. Identification of Benzodiazepine Binding Site Residues in the ?2 Subunit of the ?-Aminobutyric AcidA Receptor. *Molecular Pharmacology.* 2000;57:932-939.

38. Yehezkel Ben-Ari. Excitatory Actions of GABA during development: The Nature of the Nurture. . *Nature Reviews, Neuroscience.* 2002;3:728-739.
39. Hirata K, Matsumoto Y, Kurokawa A, et al. Possibility of Influence of Midazolam Sedation on the Diagnosis of Brain Death: Concentration of Active Metabolites after Cessation of Midazolam. *The Pharmaceutical Society of Japan.* May 15 2003 2003;123(9):811-815.
40. Nelson D. Cytochrome P450s in humans. 2003.
41. Wandel C, Bocker R, Bohrer H, et al. Midazolam is metabolized by at least three different cytochrome P450 enzymes. *British Journal of Anaesthesia.* 1994;73:658-661.
42. Eiselt R, Domanski T, Zibat A, et al. Identification and functional characterization of eight CYP3A4 protien variants. *Pharmacogenetics.* 2001;11:447-458.
43. McKenzie CA, McKinnon W, Naughton DP, et al. Differentiating midazolam over-sedation from neurological damage in the intensive care unit. . *Critical Care.* 2005;9:R32-R36.
44. Oda Y, Mizutani K, I H, et al. Fentanyl inhibits metabolism of midazolam: competitive inhibition of CYP3A4 *in vitro. British Journal of Anaesthesia.* 1999;82(6):900-903.
45. Masica A. Correlation betwwen the CYP3A-mediated oral clearance of alprazolam, midazolam and triazolam. *Clinical Pharmacology and Therapeutics.* 2004;75(2):77.
46. Tortora GJ, Grabowski SR. *Principles of Anatomy and Physiology* 10 ed. New York John Wiley & Sons, Inc.; 2003.
47. *Royal Perth Hospital Trauma Registry Report* 2004.
48. Littlejohns LR, Bader MK. Guidelines for the Management of Severe Head Injury: Clinical Applications and Changes in Practice. *Critical Care Nurse.* 2001; 21(6):48-65.
49. Seppelt I. Intracranial hypertension after traumatic brain injury. *Indian Journal Critical Care Medicine.* 2004;8(2):120-126.
50. Headwest. *Fact Sheet.* Brain Injury Association of W.A. Inc; 2005.
51. Ponsford J, Willmott C, Rothwell A, et al. Factors influencing outcome following mild traumatic brain injury in adults. *Journal of the International Neuropsychological Society.* 2000;6:568-579.
52. Alves W, Colohan A, O'Leary T, et al. Understanding posttraumatic symptoms after minor head injury. *Journal of Head Trauma Rehabilitation.* 1986;1:1-12.
53. Dikmen S, McLean AJ, Temkin N, et al. Neuropsychological and psychosocial consequences of minor head injury. *Journal of Neurology, Neurosurgery and Psychiarty.* 1986;49:1227-1232.
54. Kay T. *Neuropsychological diagnosis: Disentangling the multiple determinants of functional disability after mild traumatic brain injury.* Philadelphia: Hanley & Belfus; 1992.
55. Gronwall D, Wrightson P. Delayed recovery of intellectual function after minor head injury. *Lancet.* 1974;2:605-609.
56. Levin H, Mattis S, Ruff R, et al. Neurobehavioural outcome following minor head injury: A three centre study. *Journal of Neurosurgery.* 1987;66:234-243.
57. Rimel R, Giordani B, Barth J, et al. Disability caused by minor head injury. *Neurosurgery.* 1981;9:221-228.

58. Tentillier E, Ammirati C. Prehospital management of patients with severe head injuries. *C Ann Fr Anesthesia Reanim* 2000;19(4):275-281.
59. Littlejohns LR, Bader MK, March K. Brain Tissue Oxygen Monitoring in Severe Brain Injury, 1. *Critical Care Nurse.* 2003;23(4):17-25.
60. Alexander M. Mild traumatic brain injury: Pathophysiology, natural history, and clinical management. *Neurology.* 1995;45(7):1253-1260.
61. Servadei F, Teasdale G, Merry G. Neurosurgical Societies: Defining acute mild head injury in adults: A proposal based on prognostic factors, diagnosis and mangement. *Journal of Neurotrauma.* 2001;18(7):657.
62. Tintinalli JE, Kelen GD, Stapczynski JS. *EMERGENCY MEDICINE: A Comprehensive Study Guide.* 6 ed: McGraw Hill Companies Inc; 2004.
63. Conley R. *Head Injury.* 2nd ed. Park Ridge, IL: Roadrunner Press; 1998.
64. Roth P, Farls K. Pathophysiology of Traumatic Brain Injury. *Critical Care Nursing Quarterly.* 2000;23(3):14-24.
65. http://www.braininjury.com. Traumatic Brain Injury. *United States, Canada, England & Western Australia.*
66. W.A. BIA. Brain Injury. Brain Injury Association W.A. Inc; 2005.
67. Hutchinson P, Kirkpatrick P. Acute Head Injury for the Neurologist. *Neurol Neurosurg Psychiatry.* 2002;73:i3-i7.
68. Bouma G, Muizelaar J, Choi S, et al. Cerebral circulation and metabolism after severe traumatic brain injury: the elusive role of ischemia. *Journal of Neurosurgery.* 1991;75:685-693.
69. Della Corte F, Giordano A, Pennisi M, et al. Cerebral blood flow determination with a new DSPET device: prognostic implication in the first 48 hours after severe head injury. *Acta Neuchirurgica.* 1997;139(7):636-642.
70. Martin N, Patwardhan R, Alexander M, et al. Characterization of cerebral hemodynamic phases following severe head trauma: hypoperfusion, hyperemia and vasospasm. . *Journal of Neurosurgery* 1997;87:9-19.
71. Brink VD. Brain oxygen tension in severe head injury. *Neurosurgery.* 2000;46(4):868-878.
72. Stocchetti N, Furlan A, Volta F. Hypoxemia and Arterial Hypotension at the Accident Scene in Head Injury. *Journal of Trauma-Injury Infection & Critical Care* 1996;40(5):764-767.
73. Chestnut RM, Marshall LF, Klauber MR, et al. The Role of Secondary Brain Injury in Determining Outcome from Severe Head Injury. *The Journal of Trauma.* 1993;34(2): 216-222.
74. Choi YF, Wong TW, Lau CC. Midazolam is more likely to cause hypotension than etomidate in emergency department rapid sequence intubation. *Emergency Medicine Journal.* 2004; 21:700-702.
75. Klockgether-Radke AP, Thudium A, Frerichs A, et al. High-dose midazolam and the attenuation of the contractile response to vasoconstrictors in coronary artery segments. *European Journal of Anaesthesiology.* 2003;20:289-293.
76. Klockgether-Radke AP, Pawlowski P, Neumann P, et al. Mechanisms invovled in the relaxing effect of midazolam on coronary arteries. *European Journal of Anaesthesiology.* 2005;22:135-139.
77. Jones DJ, Stehling LC, Zauder HL. Cardiovascular response to diazepam and midazolam maleate in the dog. *Anesthesiology.* 1979;51:430-434.
78. Reves JG, Kissin I, Fournier S. Negative inotropic effects of midazolam. *Anesthesiology* 1984;60:517-518.

79. Reves JG, Samuelson PN, Lewis S. Midazolam maleate induction in patients with ischaemic heart disease: haemodynamic observations. . *Canadian Anesthetists' Society Journal.* 1979;26:402-409.
80. Samuelson PN, Reves JG, Kouchoukos NT, et al. Hemodynamic Responses to Anesthetic Induction with Midazolam or Diazepam in Patients with Ischemic Heart Disease. *Anesthesia and Analgesia.* 1981;60:802-809.
81. Marty J, Gauzit R, Lefevre P. Effects of diazepam and midazolam on bar oreflex control of heart rate and on sympathetic activity in humans. *Anesthesia and Analgesia.* 1986;65:113-119.
82. Chang KSK, Feng MD, Davis RG. Midazolam produces vasodilation by mixed endothelium-dependent and independent mechanisms. *Anesthesia and Analgesia.* 1994;78:710-717.
83. Shunichiro Y, Yuichi K, Nozomu Y. Effects of Midazolam on Contractions in Smooth Muscle of the Rabbit Mesenteric Artery. *Department of Anesthesiology and Critical Care Medicine.* 1997;84:199-205.
84. Servadei F, Teasdale G, Merry G. Neurotraumatology Committee of the World Federation of Neurosurgical Societies: Defining acute mild head injury in adults: A proposal based on prognostic factors, diagnosis, and mangement. *J Neurotrauma.* 2001;18(7):657.
85. Kirsch TD, Lipinski CA. *Emergency Medicine; A comprehensive study guide; Head Injury.* 6 ed. North America: McGraw-Hill Companies, Inc; 2004.
86. Bodian CA, Freedman G, Hossain S, et al. The visual Analog Scale for Pain. *Anesthesiology.* 2000; 95::1356-1361.
87. Lord BA, Parsell B. Measurement of Pain in the Prehospital Setting Using a Visual Analogue Scale. *Prehospital and Diaster Medicine.* 2003;18(4):353-358.
88. Bird J. Assessing pain in older people. *Nursing Standard.* 2005;19:45-52.
89. Maio R, Garrison H, Spaite D, et al. Emergency Medical Services Outcomes Project (EMSOP) IV: Pain Measurement in Out-of-Hospital Outcomes Research. *Annals of Emergency Medicine.* 2002;40(2):172-179.
90. Martin N, Patwardhan R, Alexander M. Characterization of cerebral hemodynamic phases following severe head trauma: hypoperfusion, hyperemia and vasospasm. *Journal of Neurosurgery.* 1997(87):9-19.
91. Berggren L, Eriksson I, Mollen holt P, et al. Changes in respiratory pattern after repeated doses of diazepam and midazolam in healthy subjects. *Acta Anaesthesiol Scand.* 1987;8(Nov 31):667-672.
92. Bouma G, Muizelaar J, Choi S. Cerebral circulation and metabolism after severe traumatic brain injury: the elusive role of ischemia. *Journal of Neurosurgery.* 1991(75):685-693.
93. Kay T. *Neuropsychological diagnosis.* Philadelphia: Hanley & Belfus; 1992.

Appendix. 1



Appendix 2

ST JOHN AMBULANCE AUSTRALIA
W.A. AMBULANCE SERVICE INC.

Clinical Practice Guideline 20
September, 2004

HEAD TRAUMA:

Assume cervical injury until proved otherwise refer to CPG 31 (Indications for Spinal Precautions).

Specific information needed:

History:

- Mechanism of injury.
- Estimate of force involved, potential for concealed injury.
- **Change** in level of consciousness since injury.
- Amnesia for events prior to and/or following trauma.
- With motorcycle, bicycle and industrial accidents, was a helmet worn?
- How does patient feel? Movement, sensation, numbness, tingling.
- Brief relevant past history - medical problems, medications.

Specific physical findings:

- Vital Signs *(note respiratory pattern and rate).*
- Level of consciousness (GCS). When assessing children less than 14 years of age use AVPU.
- Neurological examination, including pupils and response to stimuli, and record findings. **NOTE differences** between sides. (Skill 103)
- External evidence of trauma (abrasions, lacerations, etc.).

Management:

Danger, Response, Airway, Breathing, Circulation Disability Exposure.

Jaw thrust or oropharyngeal airway as needed. Noisy breathing is **obstructed** breathing.

Be alert for airway problems and/or seizure activity. If indicated, consider advanced airway management.

Oxygen, high concentration or 100% *(ventilate if necessary)* to maintain oxygen saturation of **at least 90%.**

Immobilise cervical spine with collar and sandbags. Patients with suspected head/neck injury may be agitated and may not tolerate application of collars. Do not force collars on under these circumstances.

Scalp bleeding may be stopped by direct local pressure. If the underlying skull is unstable, pressure should be applied to the periphery of the laceration over intact bone, using a large pad.

If patient has other serious injuries, these will have priority.

If evidence of poor peripheral perfusion, administer i/v fluid to maintain cerebral perfusion and conscious level Try to maintain a systolic blood pressure of at least 90 mmHg. Consider MAST if no other option is available.

For longer transport times, if practical manage patient with upper body raised 30^0 to decrease cerebral oedema *(unless hypotensive)*. Ensure head neck alignment is maintained.

If altered mental state, check BSL.

Monitor Vital Signs and level of consciousness at scene and during transport.

STATUS CHANGES ARE IMPORTANT. Record findings.

Specific precautions/notes:

- The most important information you provide for the hospital is **TIME SEQUENCE OF LEVEL OF CONSCIOUSNESS.**
- Is the patient stable, deteriorating or improving?
- Assume cervical spine injury in **all patients** with significant head trauma.
- Any patient with even a transitory loss of consciousness should be assumed to have sustained significant trauma to the brain.

IF PATIENT WITH HEAD TRAUMA IS IN SHOCK, LOOK ELSEWHERE FOR

POSSIBLE CAUSES. SHOCK IS PROBABLY NOT DUE TO HEAD INJURY.

Additional Notes

Restlessness/aggressiveness can be a sign of hypoxia. **Cerebral hypoxia is the most frequent cause of death in head injury.** A GOOD AIRWAY IS ABSOLUTELY VITAL.

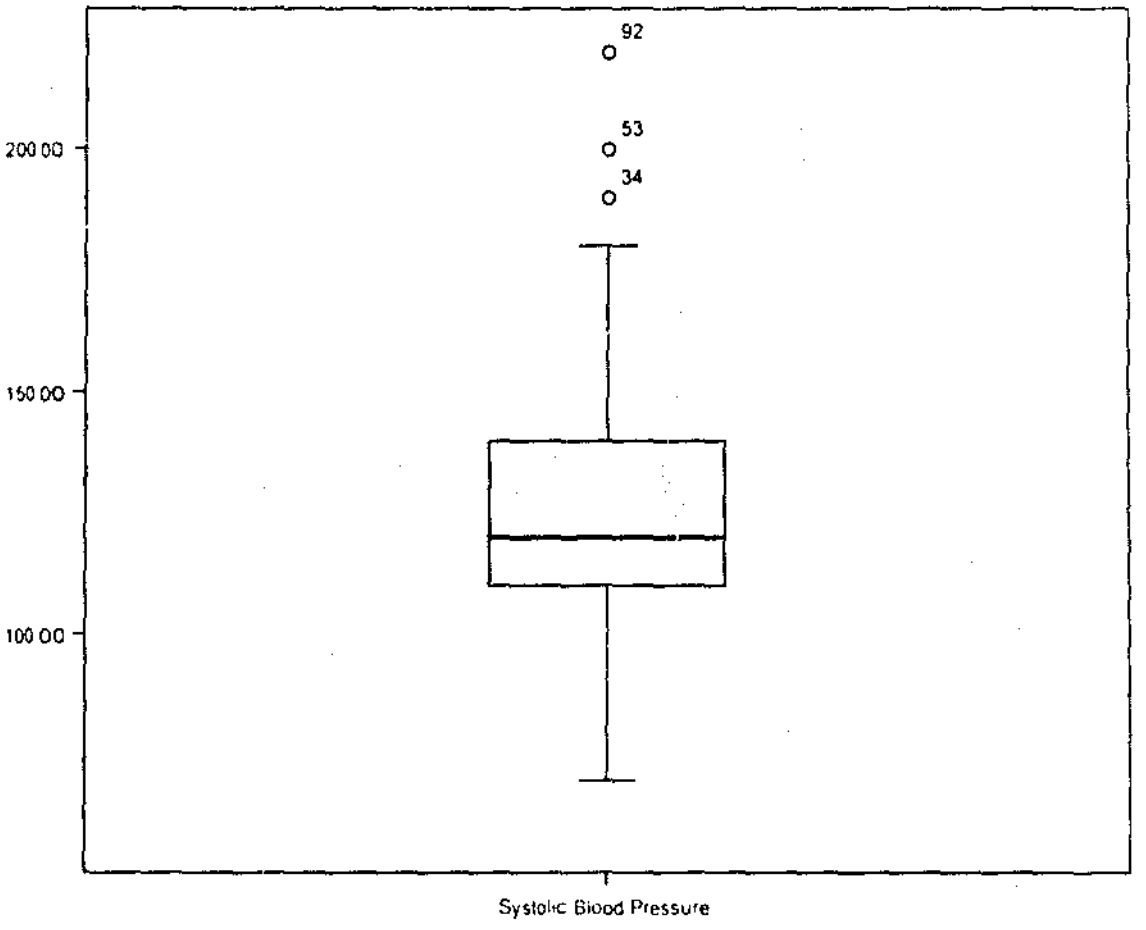
The head injured patient with a compromised airway should be managed in the lateral position while ensuring spinal precautions and providing high concentration O_2 and ventilatory support if required.

It should be an officer's LAST RESORT to administer a sedating agent to a head injured patient. Sedating agents such as benzodiazepines can precipitate large falls in blood pressure and depress respirations. These factors contribute to poor patient outcome significantly increasing mortality. Sedation may be used in small doses when there is **no other option** to facilitate safe and rapid transport.

An officer should NEVER attempt to sedate for the purpose of intubating head injured patients. This requires large doses of sedation and increases risk of death by three to four times.

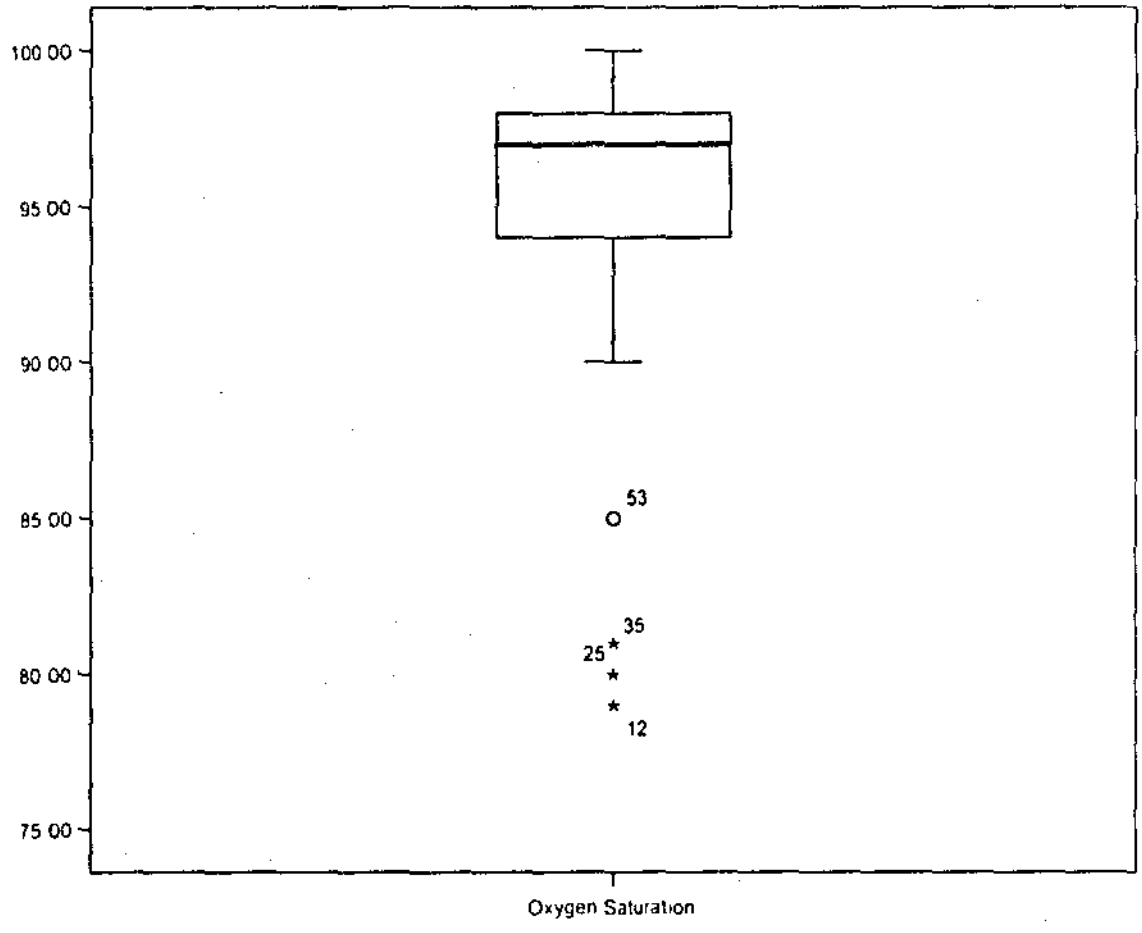
Appendix 3.

Box plot demonstrates normality for Systolic Blood Pressure in midazolam/non midazolam cohort



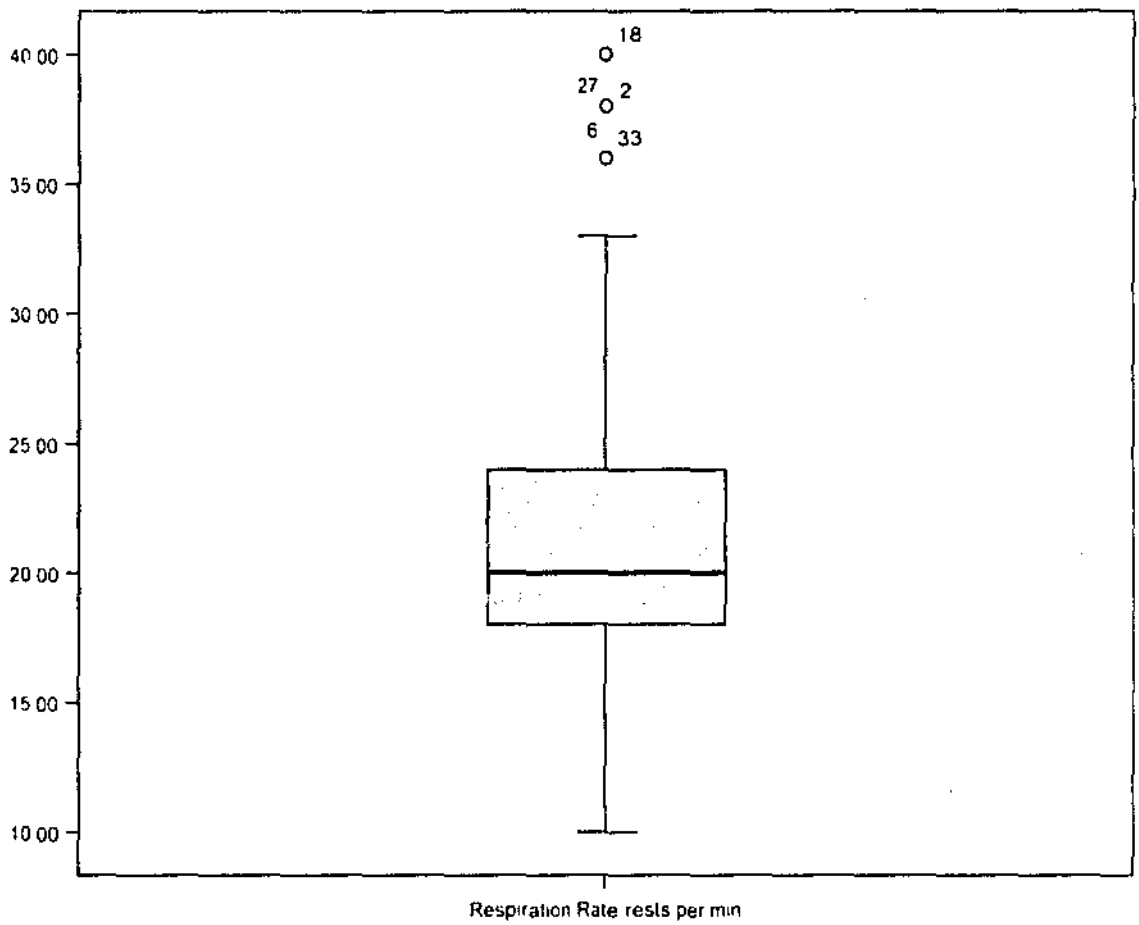
Appendix 4.

Box plot demonstrates normality for Oxygen Saturation in midazolam/non midazolam cohort



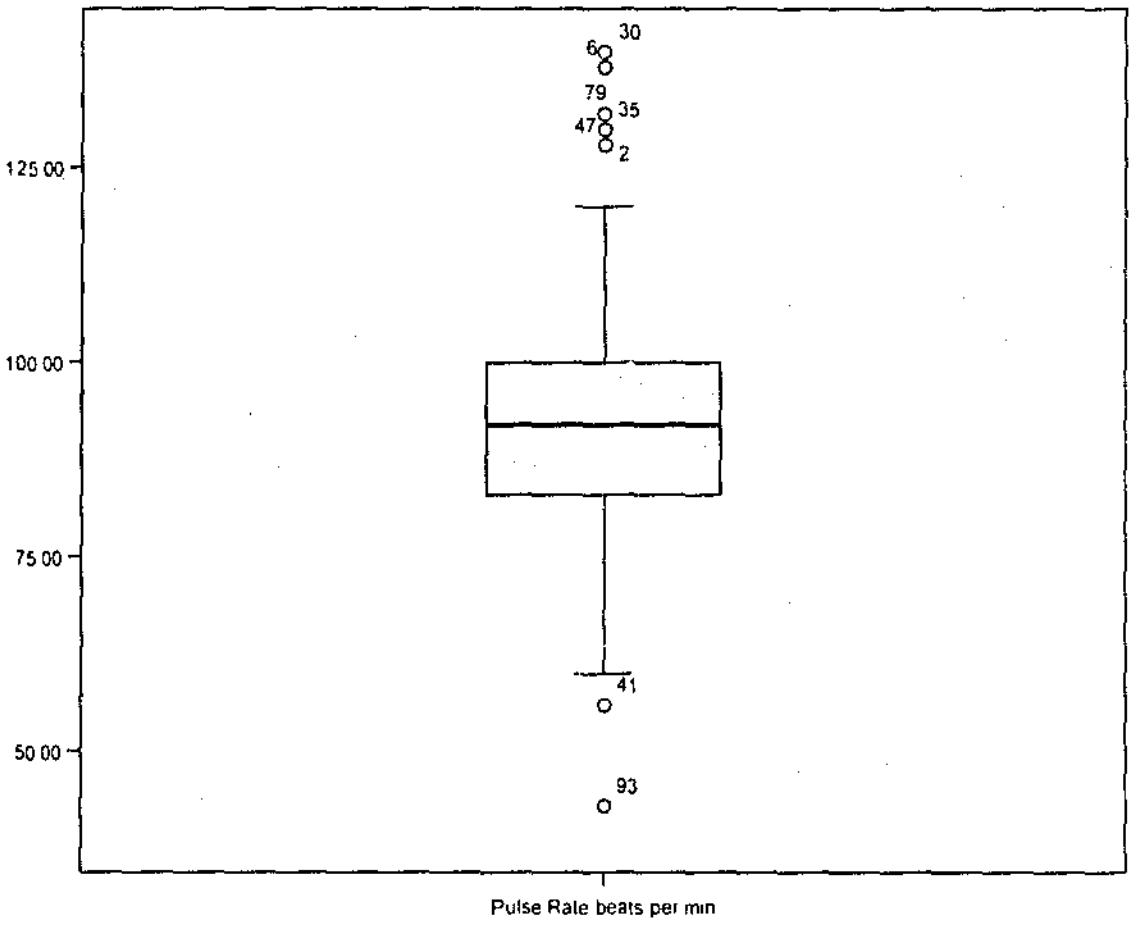
Appendix 5.

Box plot demonstrates normality for Respiration Rate in midazolam/non midazolam cohort



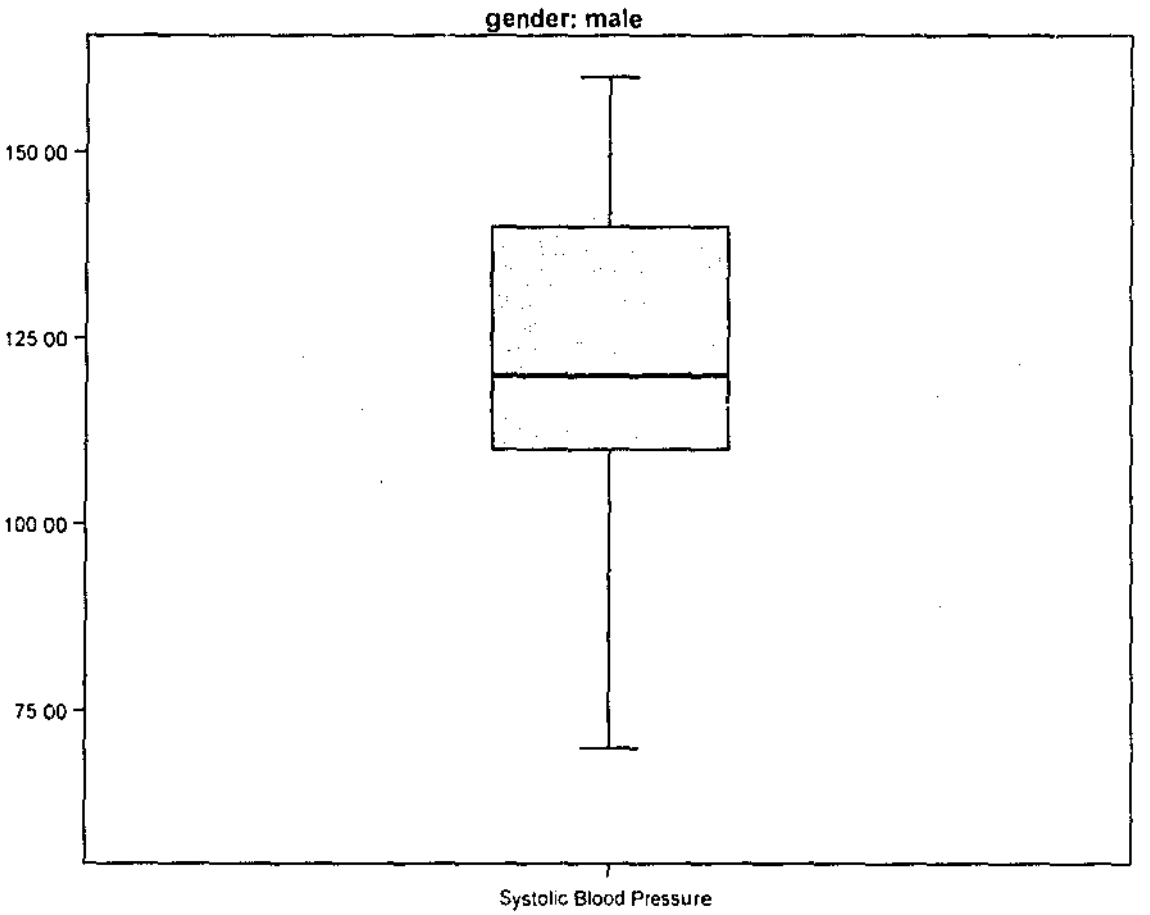
Appendix 6.

Box plot demonstrates normality for Pulse Rate in midazolam/non midazolam cohort



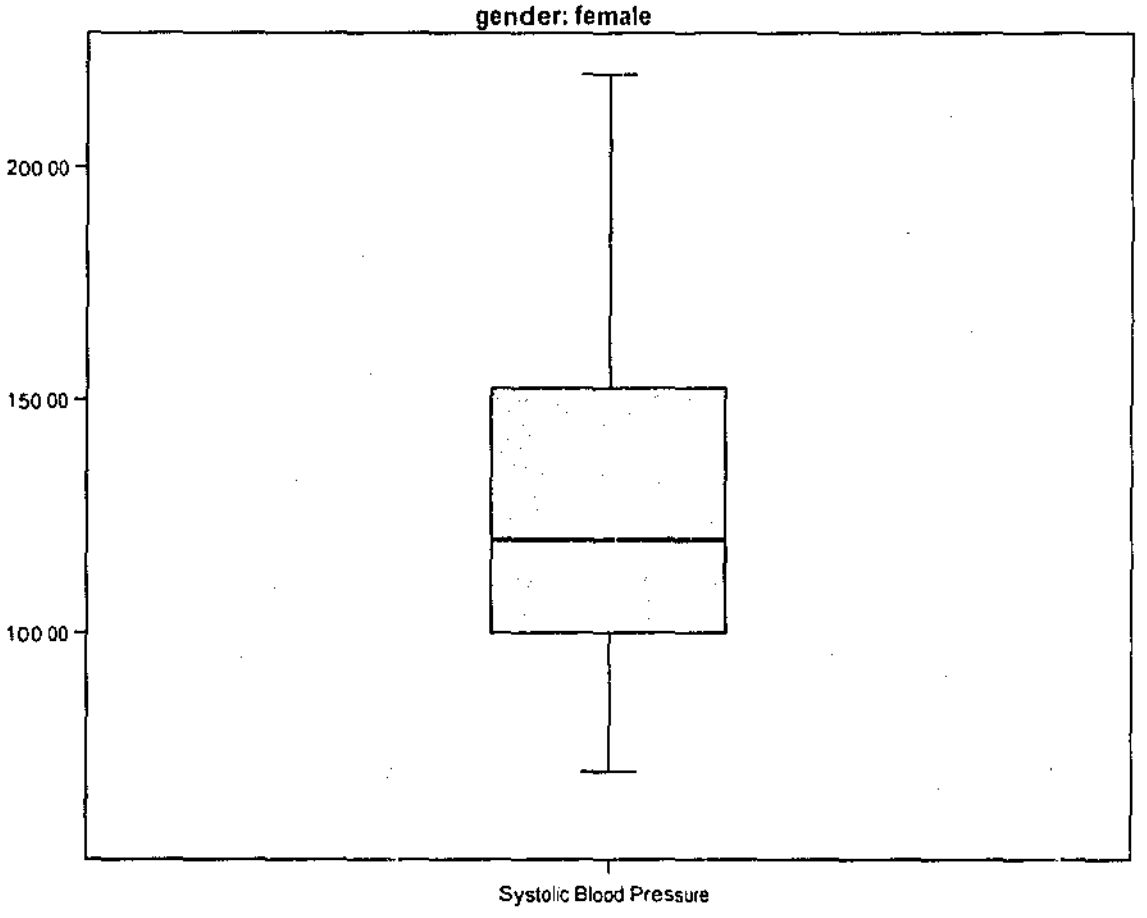
Appendix 7.

Box plot demonstrates normality for Systolic Blood Pressure in males



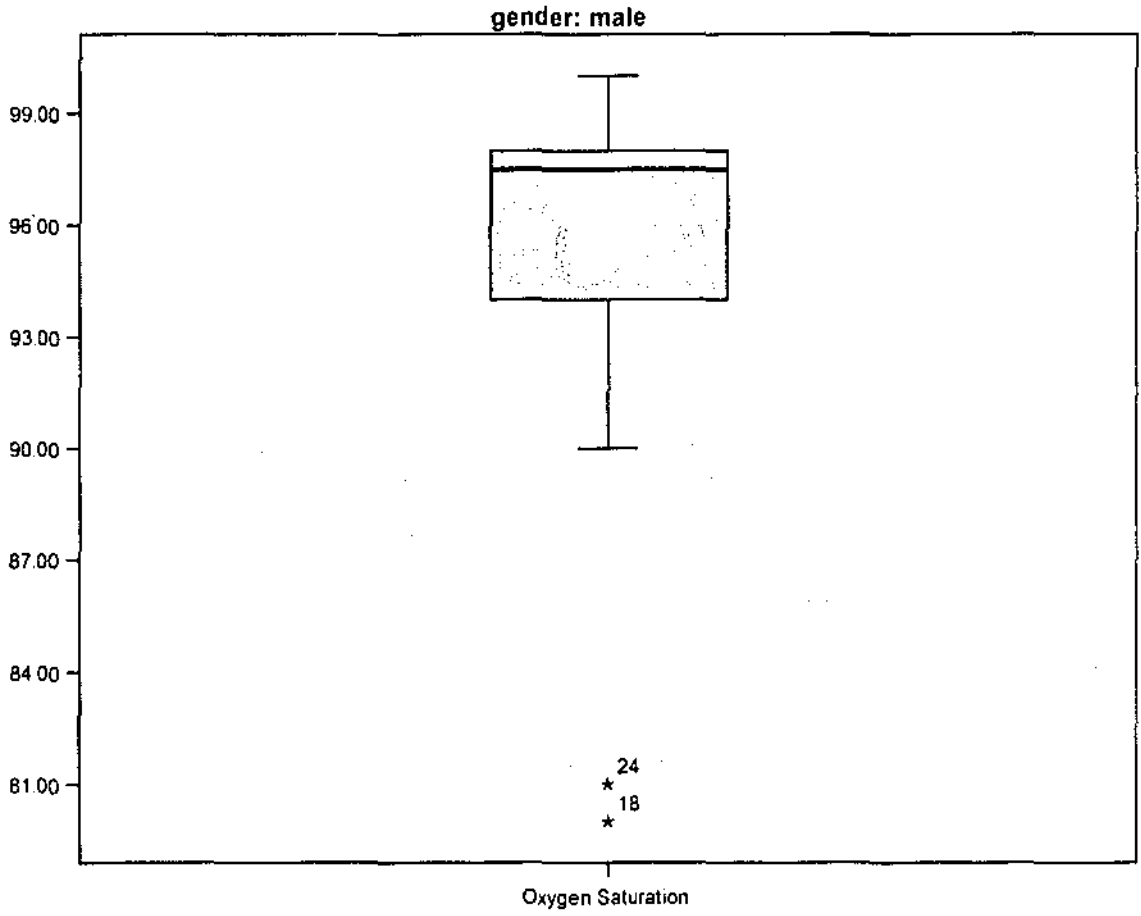
Appendix 8.

Box plot demonstrates normality for Systolic Blood Pressure in females



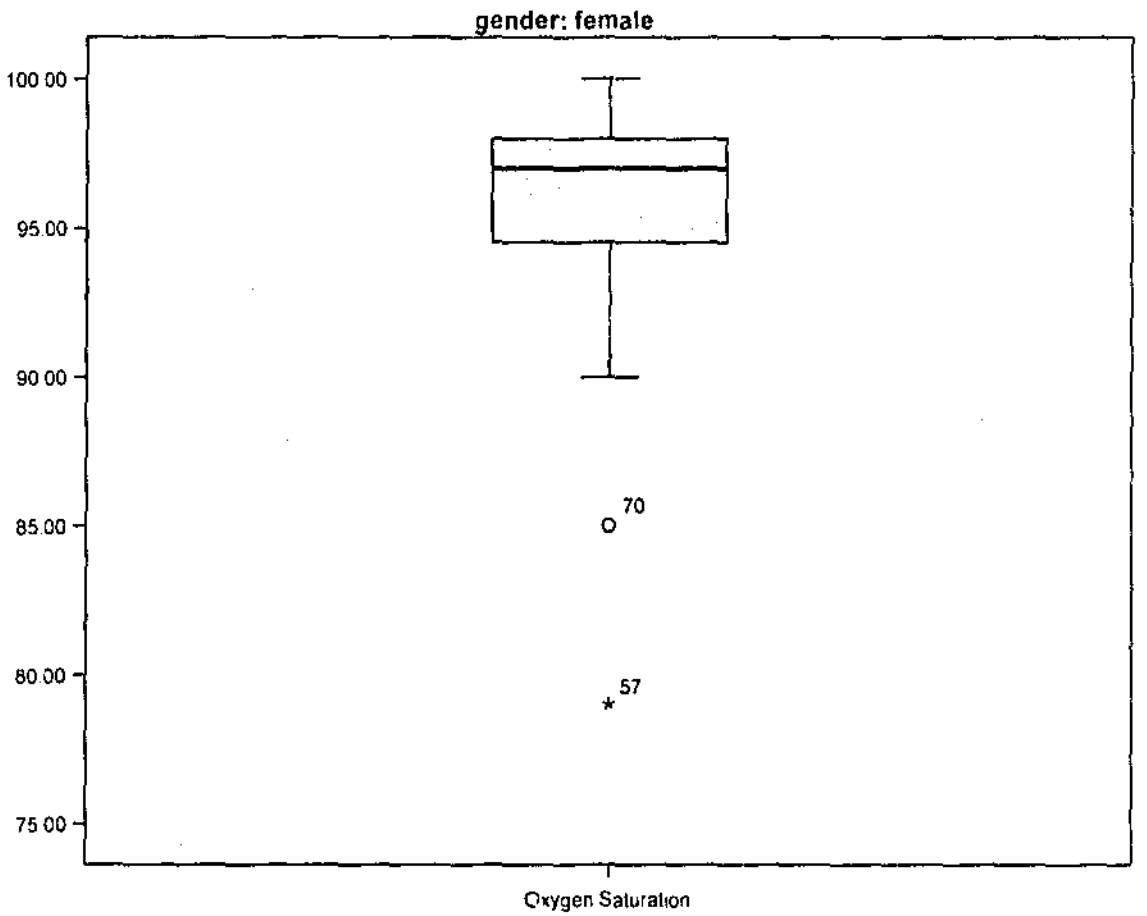
Appendix 9.

Box plot demonstrates normality for Oxygen Saturation in males



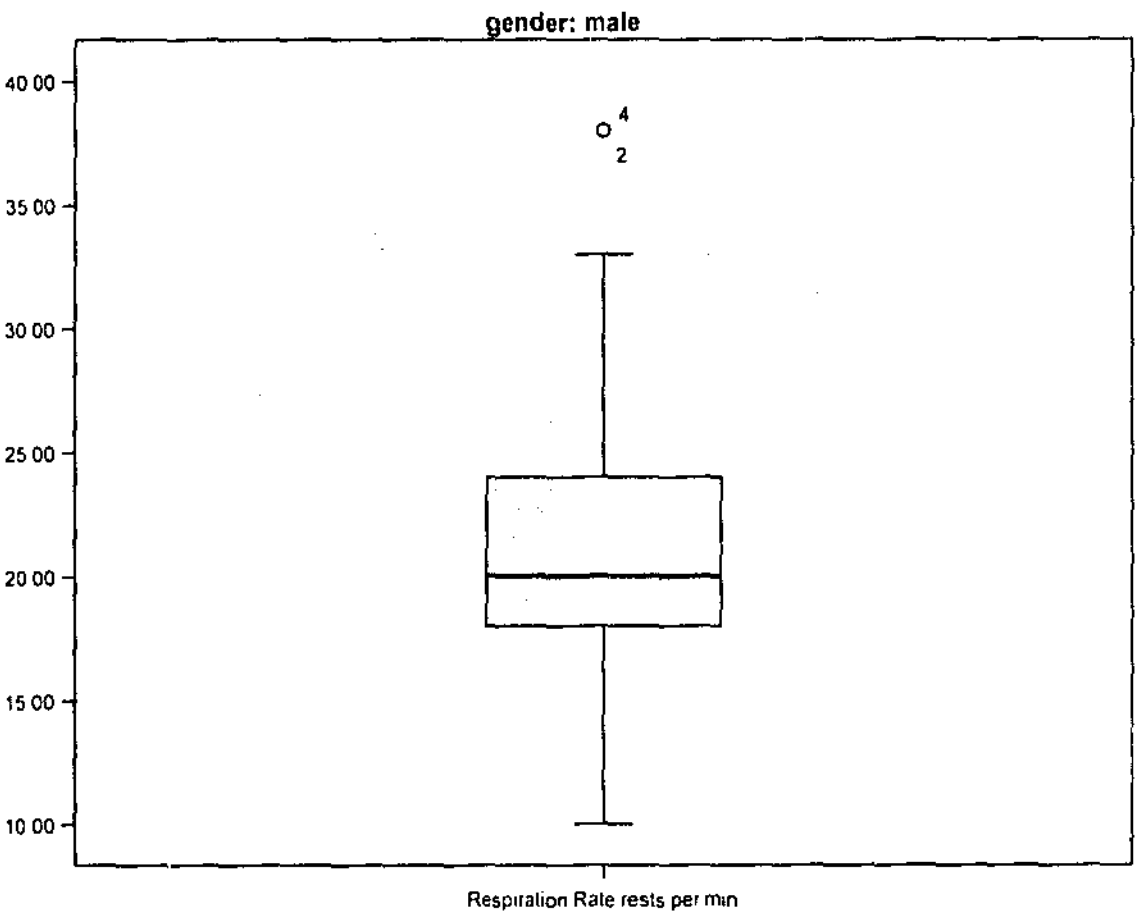
Appendix 10.

Box plot demonstrates normality for Oxygen Saturation in females



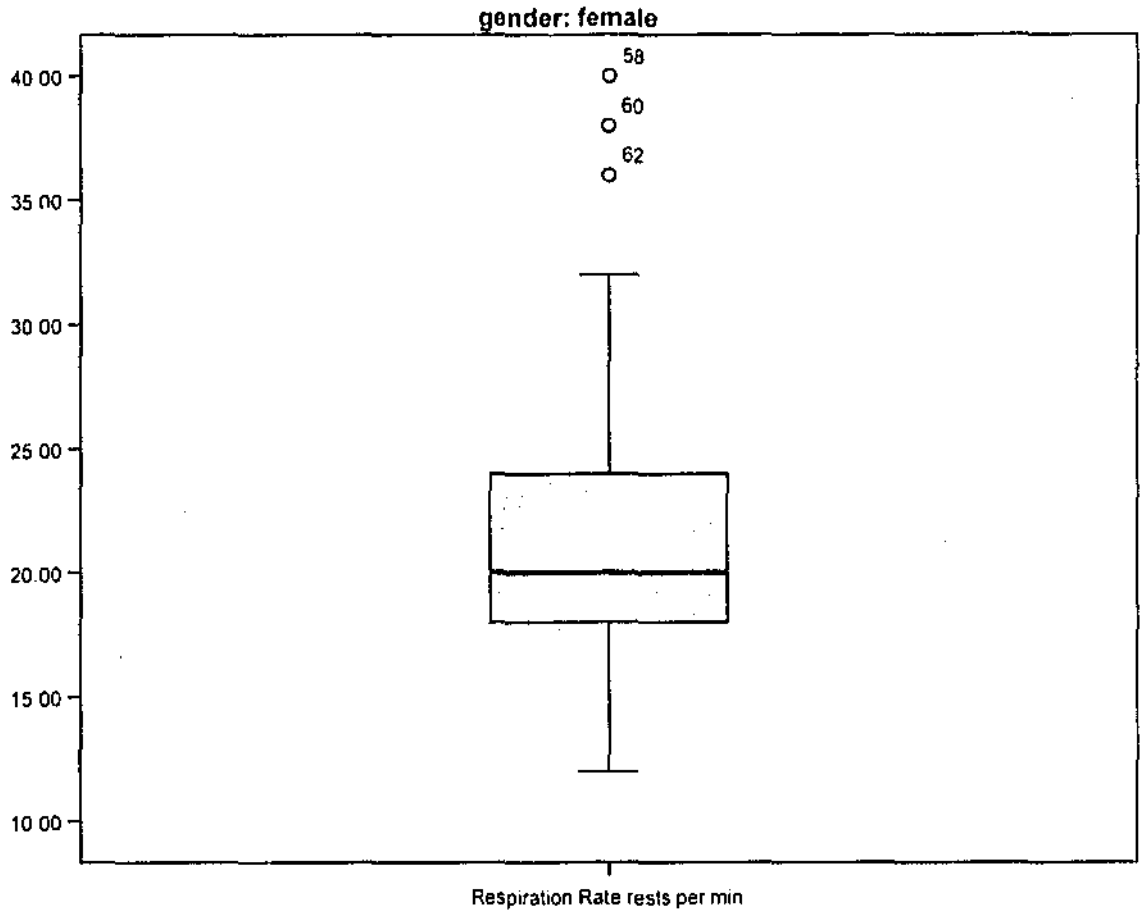
Appendix 11.

Box plot demonstrates normality for Respiration Rate in males



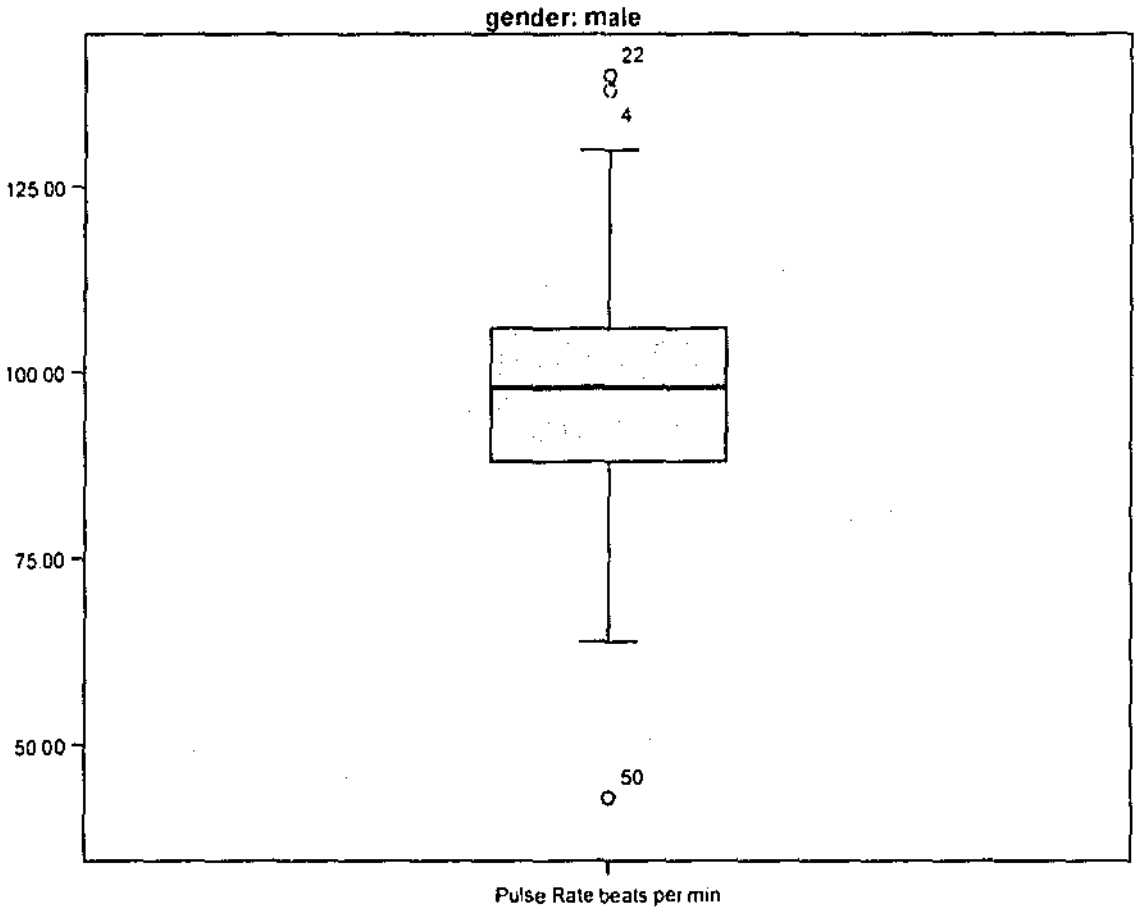
Appendix 12.

Box plot demonstrates normality for Respiration Rate in females



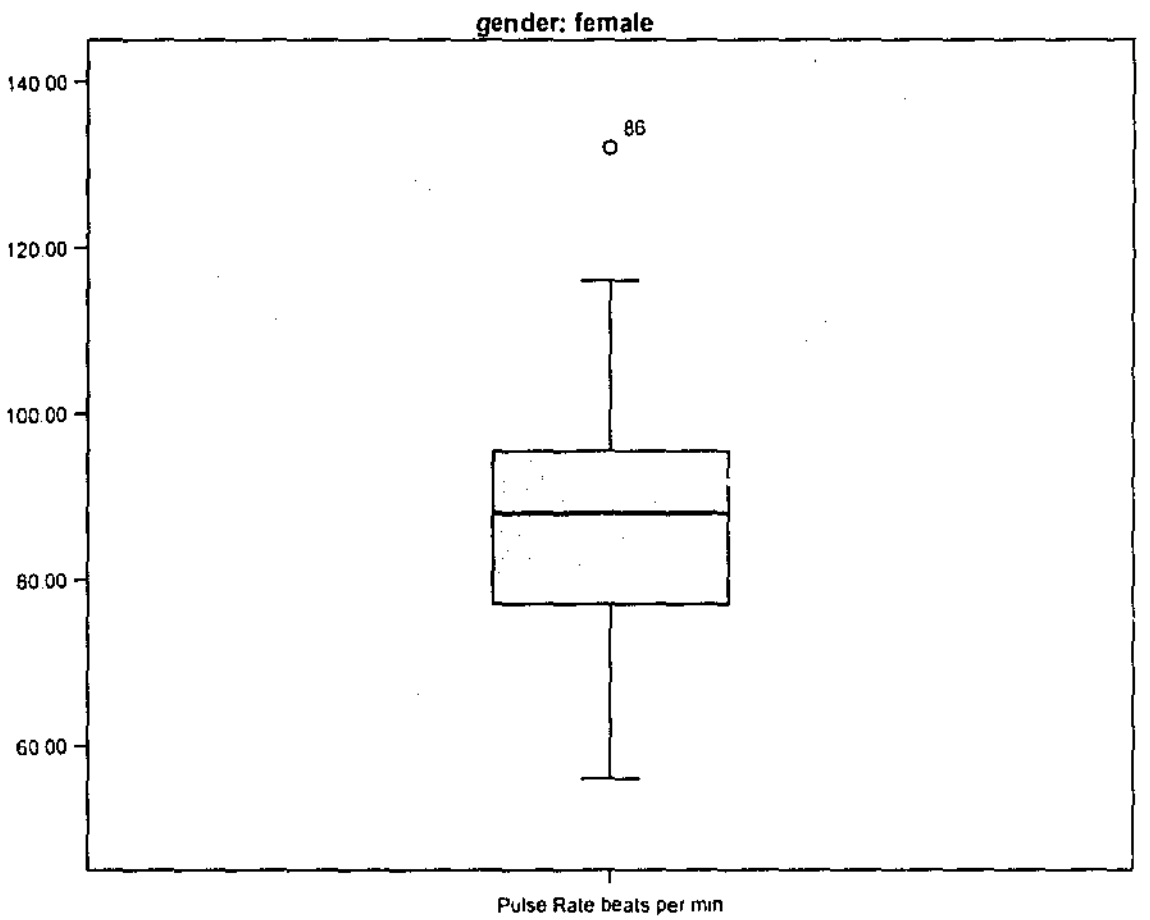
Appendix 13.

Box plot demonstrates normality for Pulse Rate in males



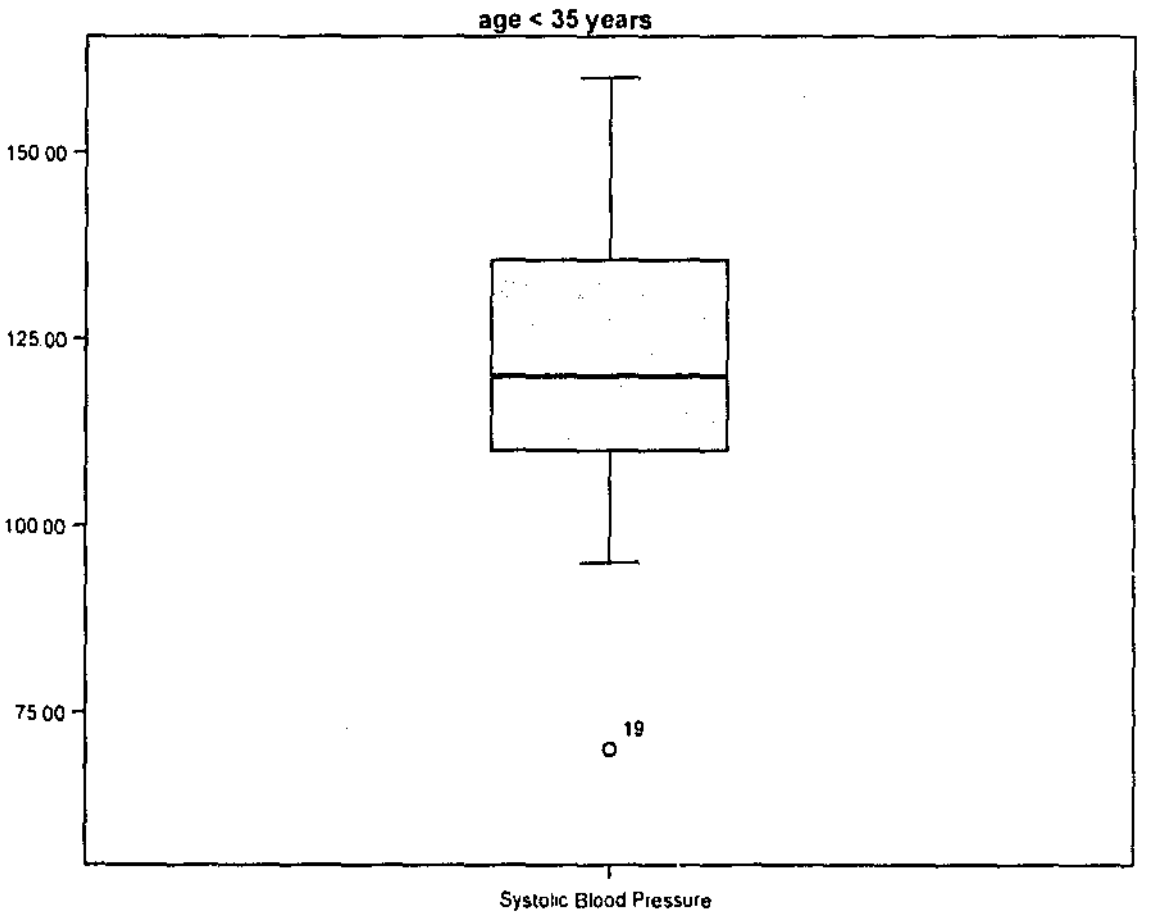
Appendix 14.

Box plot demonstrates normality for Pulse Rate in females



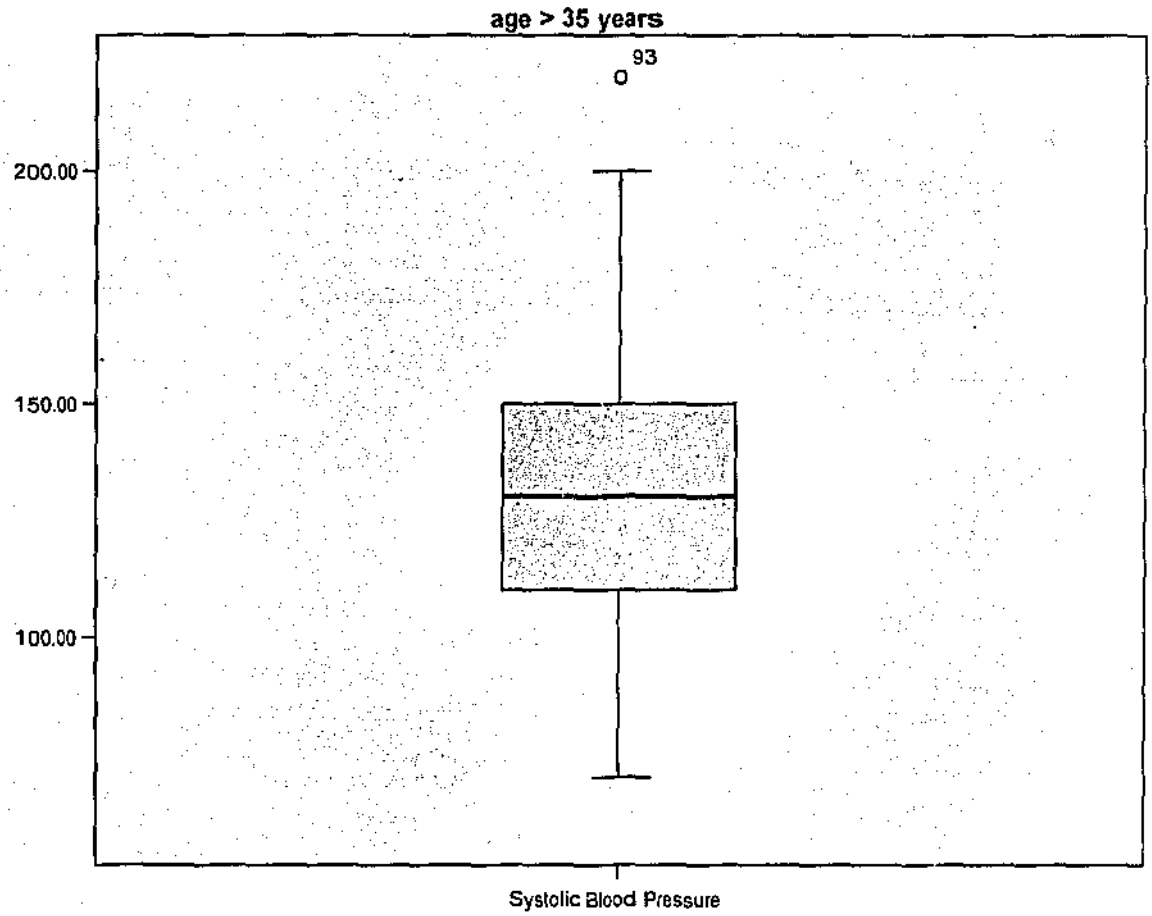
Appendix 15.

Box plot demonstrates normality for Systolic Blood Pressure in age category less than 35 years



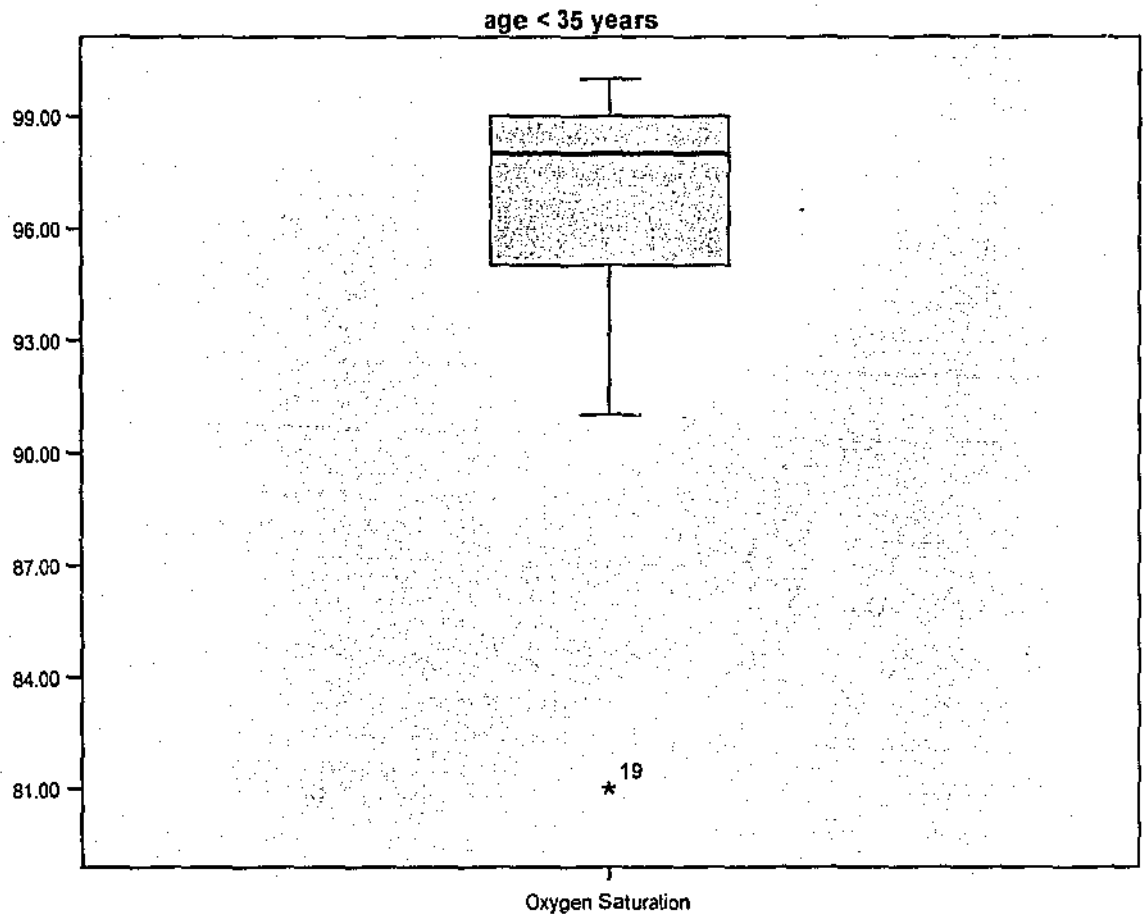
Appendix 16.

Box plot demonstrates normality for Systolic Blood Pressure for age category greater than 35 years



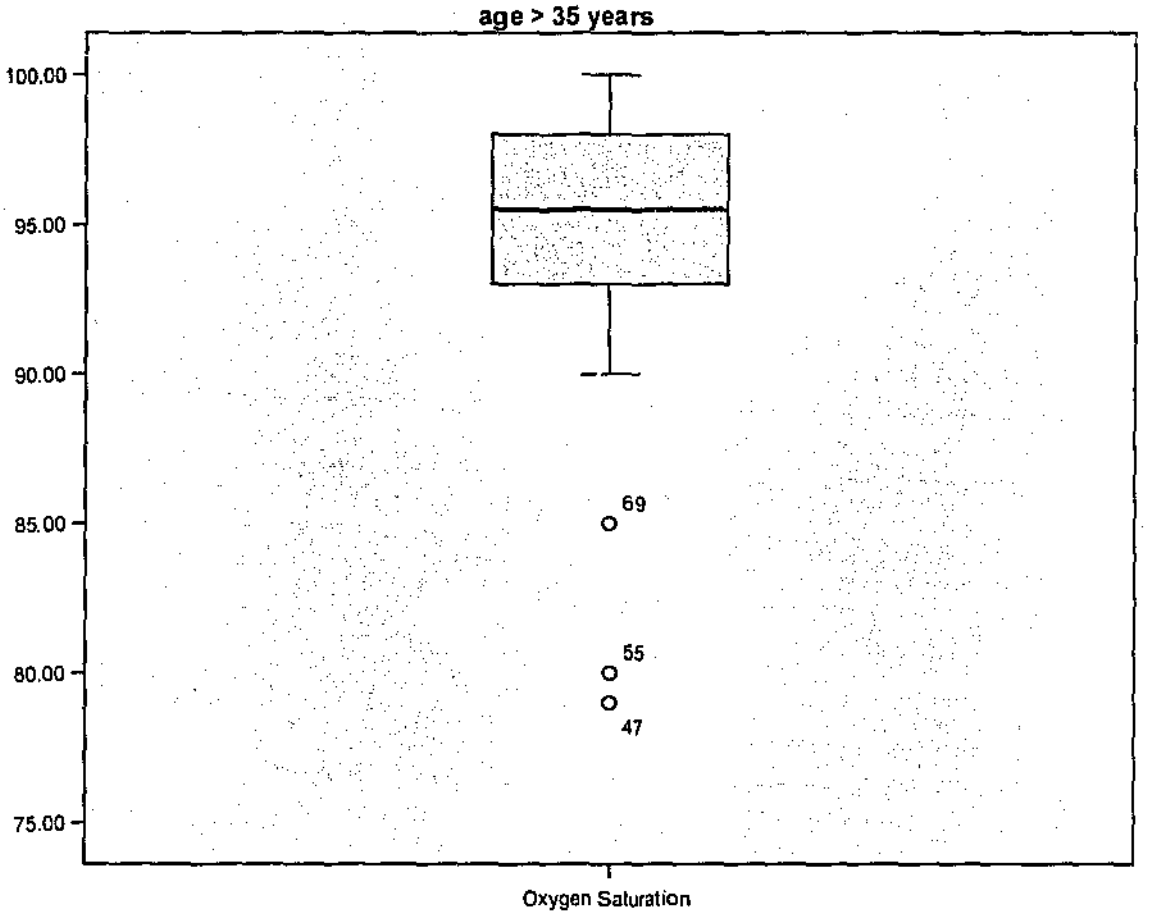
Appendix 17.

Box plot demonstrates normality for Oxygen Saturation for age category less than 35 years



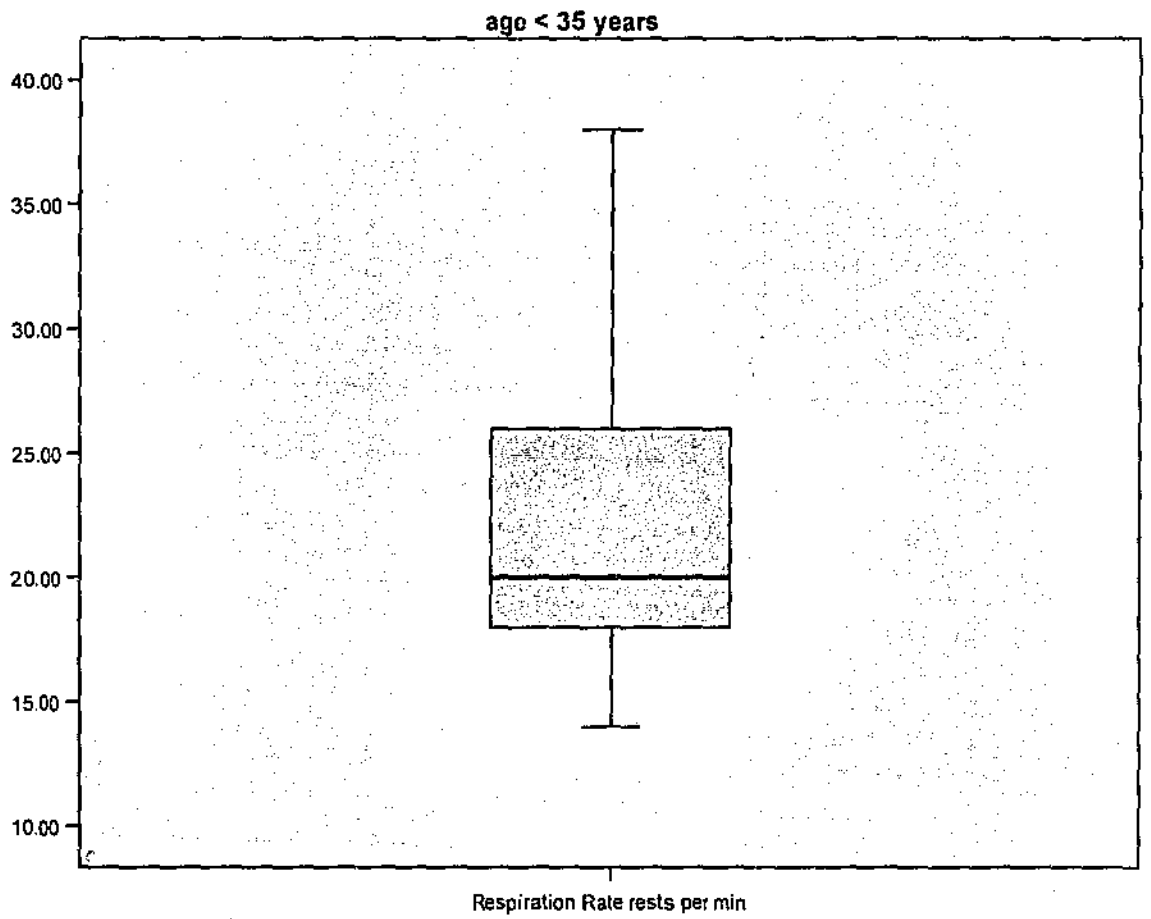
Appendix 18.

Box plot demonstrates normality for Oxygen Saturation for age category greater than 35 years



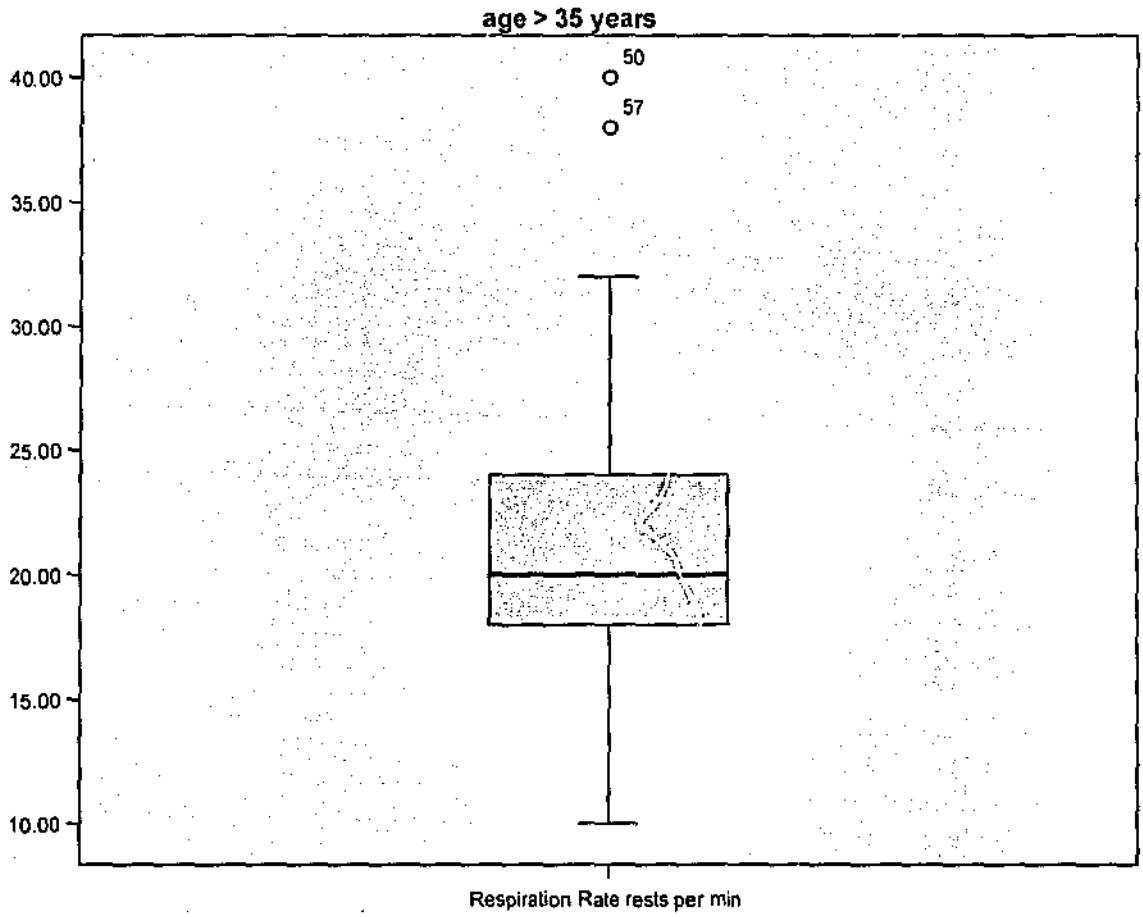
Appendix 19.

Box plot demonstrates normality for Respiration Rate for age category less than 35 years



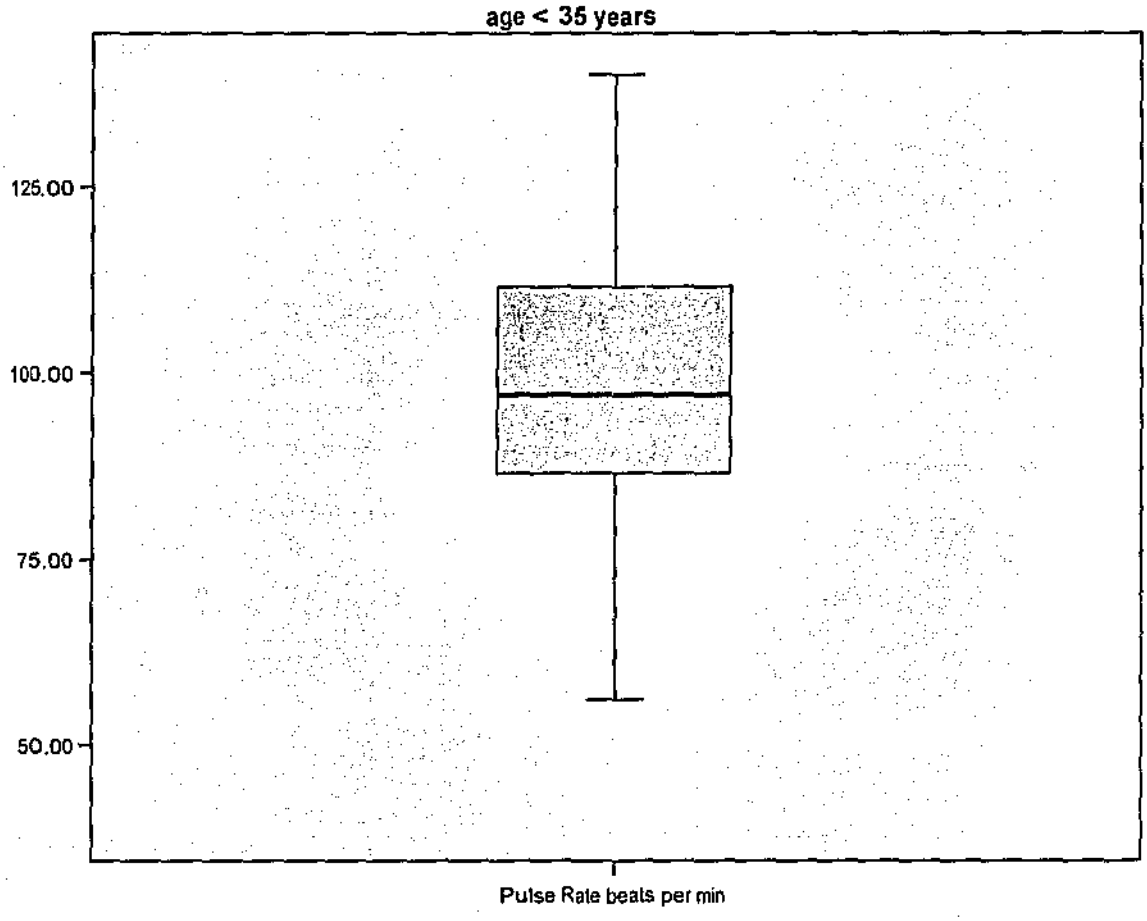
Appendix 20.

Box plot demonstrates normality for Respiration Rate for age category greater than 35 years



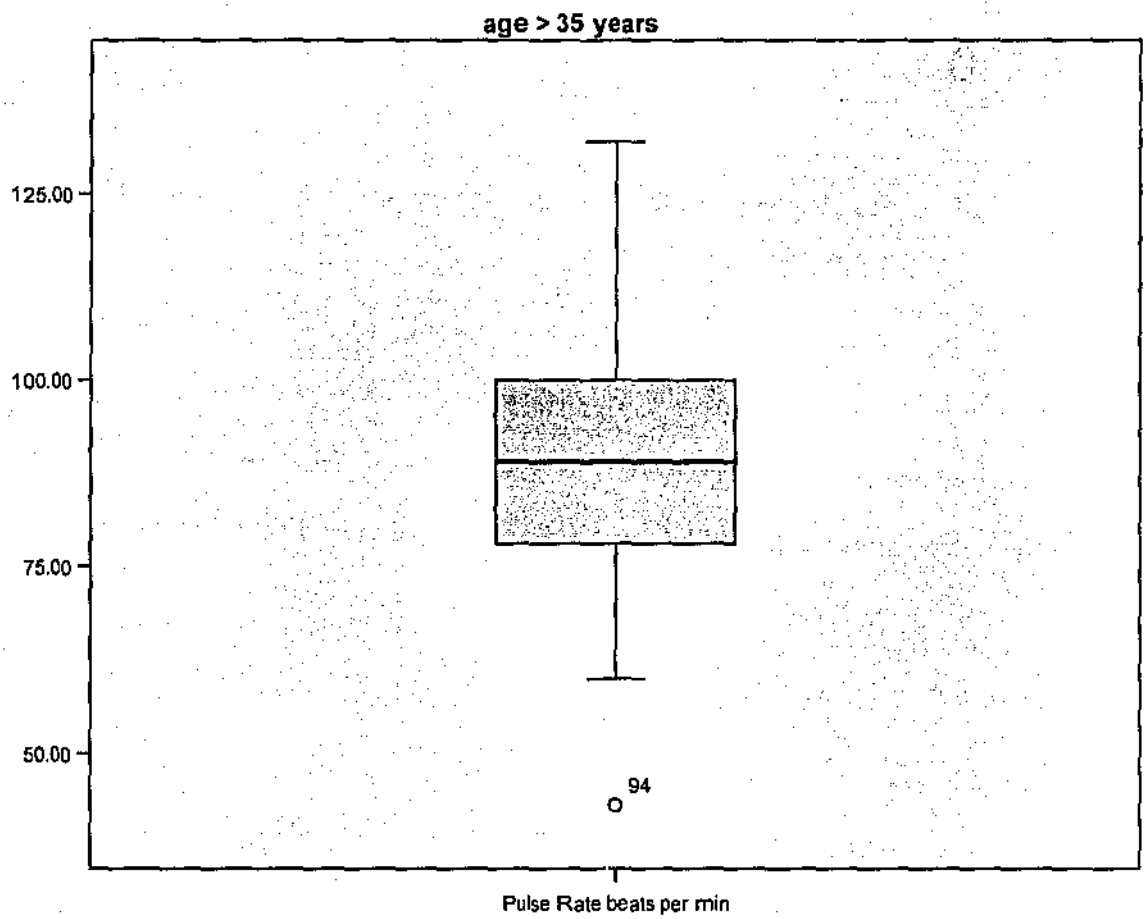
Appendix 21.

Box plot demonstrates normality for Pulse Rate for age category less than 35 years



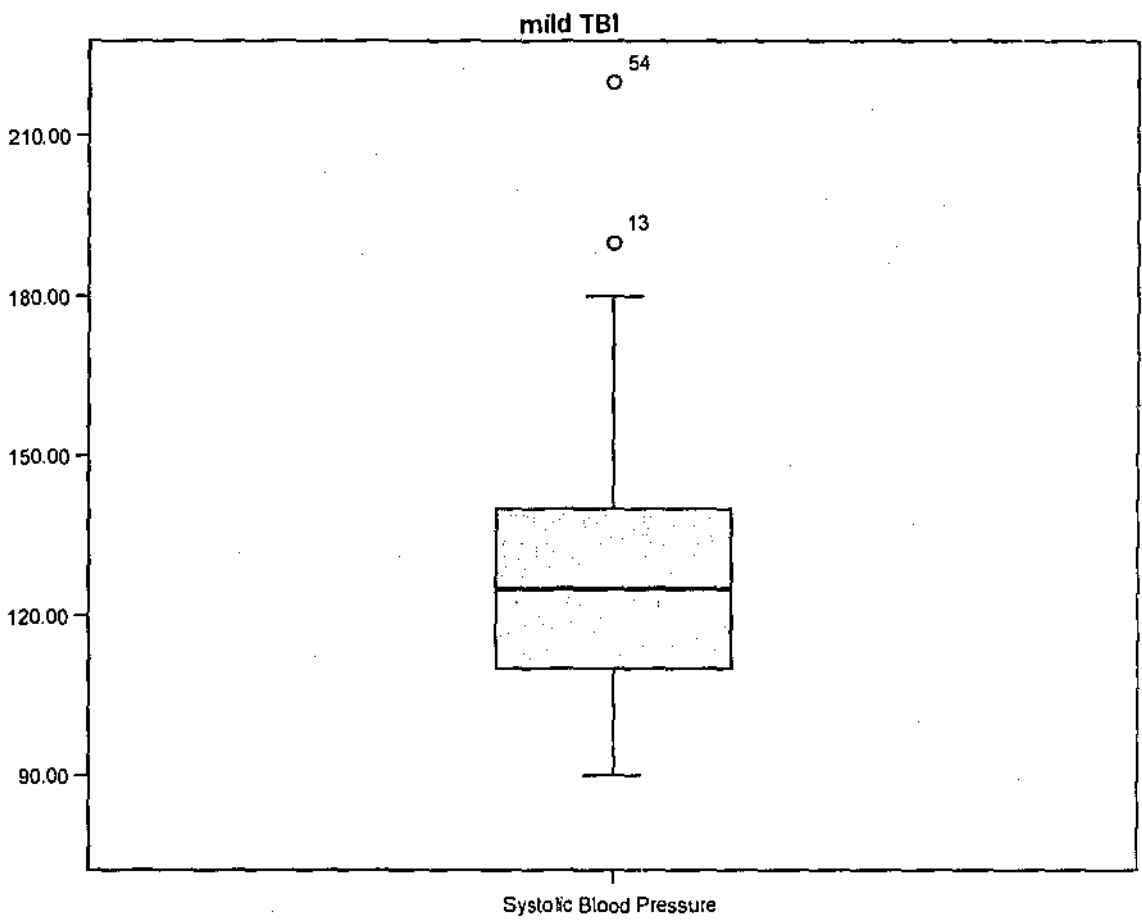
Appendix 22.

Box plot demonstrates normality for Pulse Rate for age category greater than 35 years



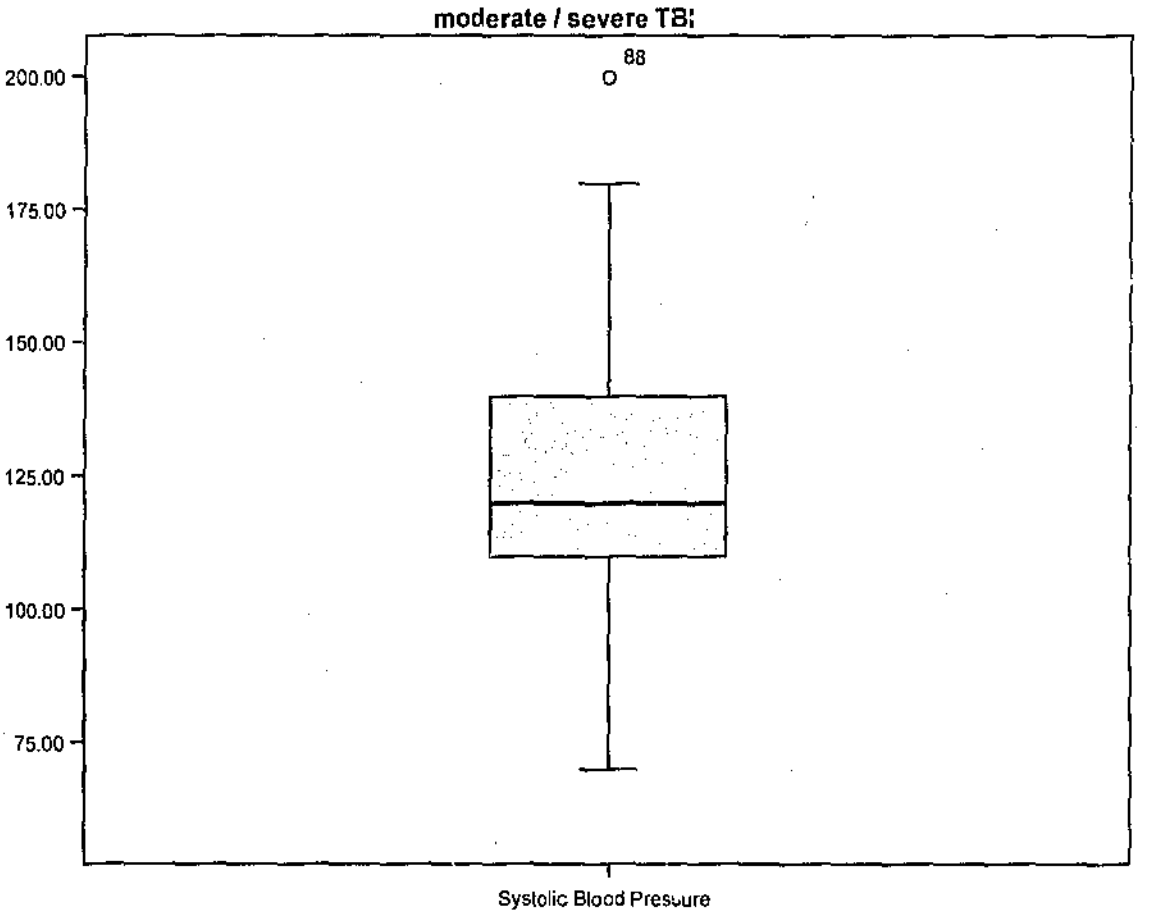
Appendix 23.

Box plot demonstrates normality for Systolic Blood Pressure in mild TBI cases



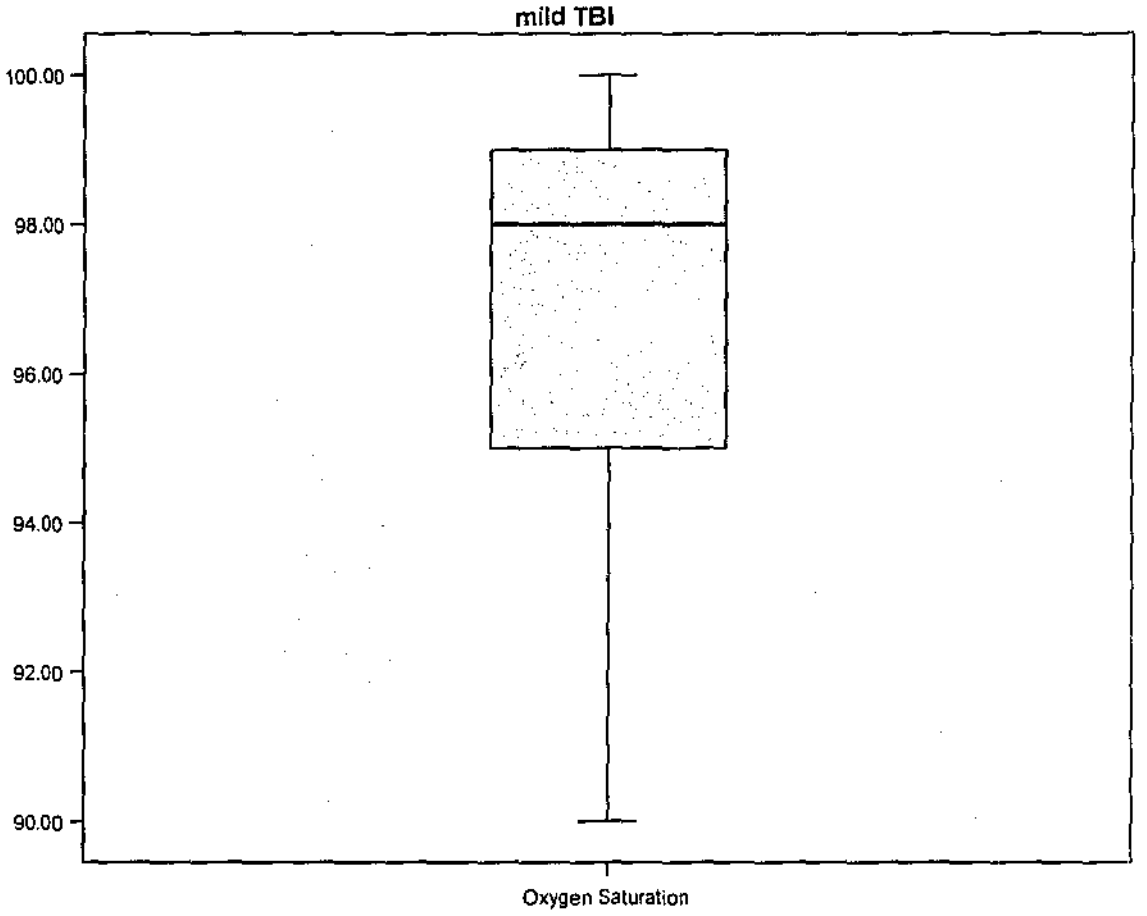
Appendix 24.

Box plot demonstrates normality for Systolic Blood Pressure in moderate/severe TBI cases



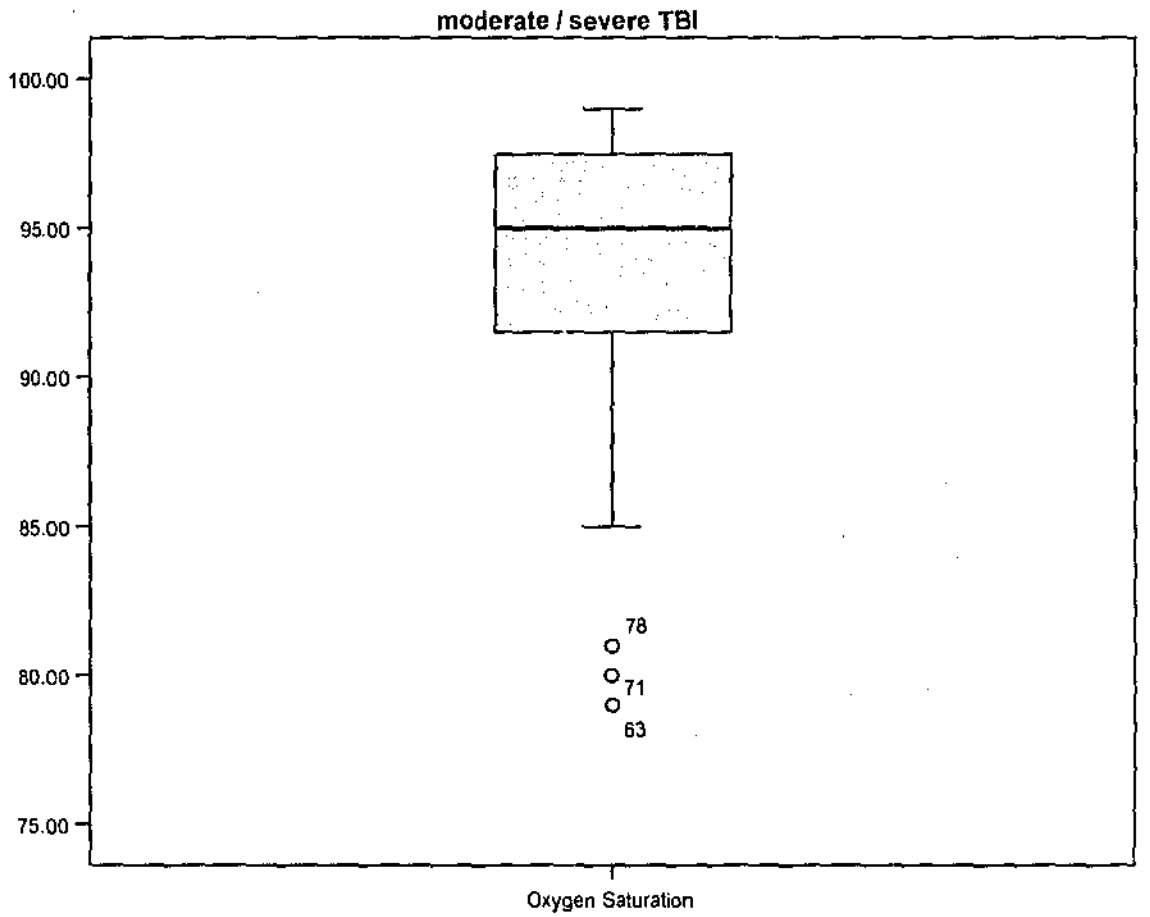
Appendix 25.

Box plot demonstrates normality for Oxygen Saturation in mild TBI cases



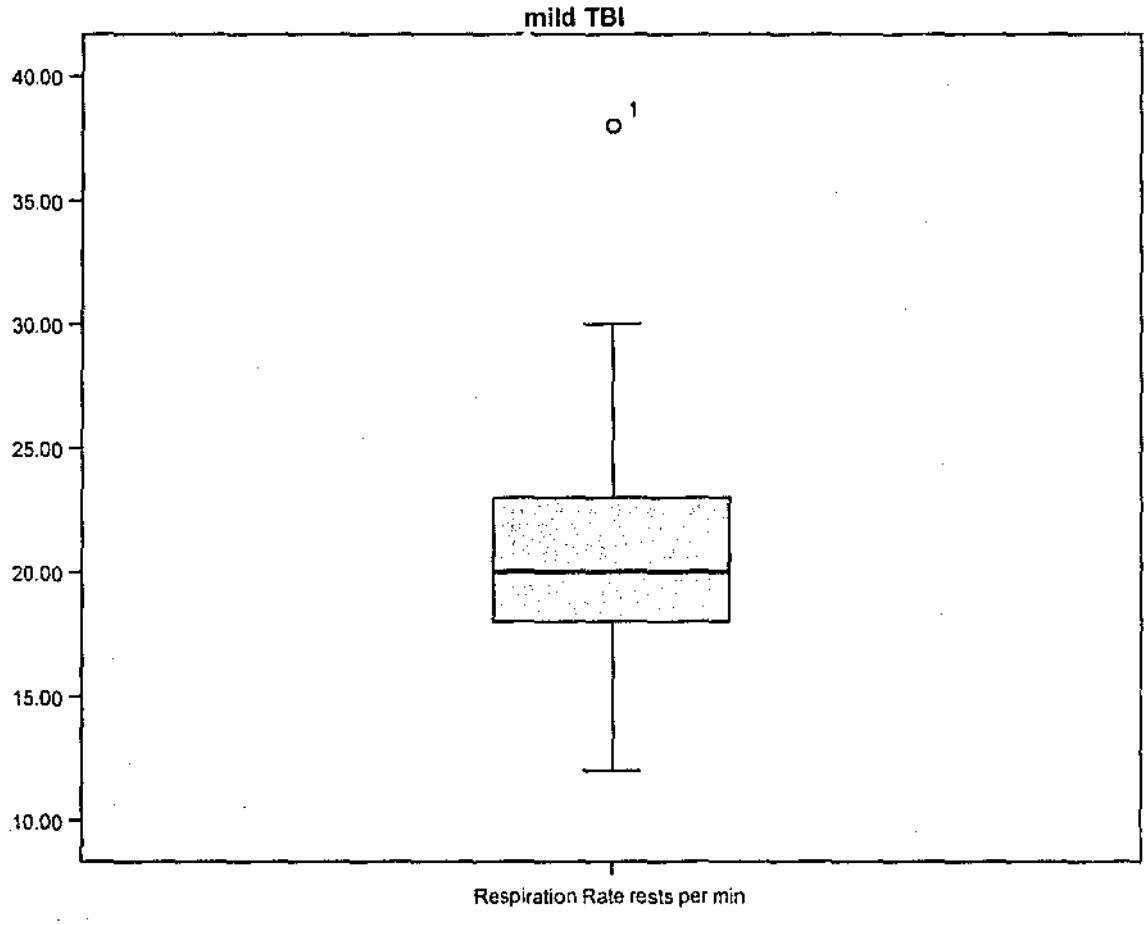
Appendix 26.

Box plot demonstrates normality for Oxygen Saturation in moderate/severe TBI cases



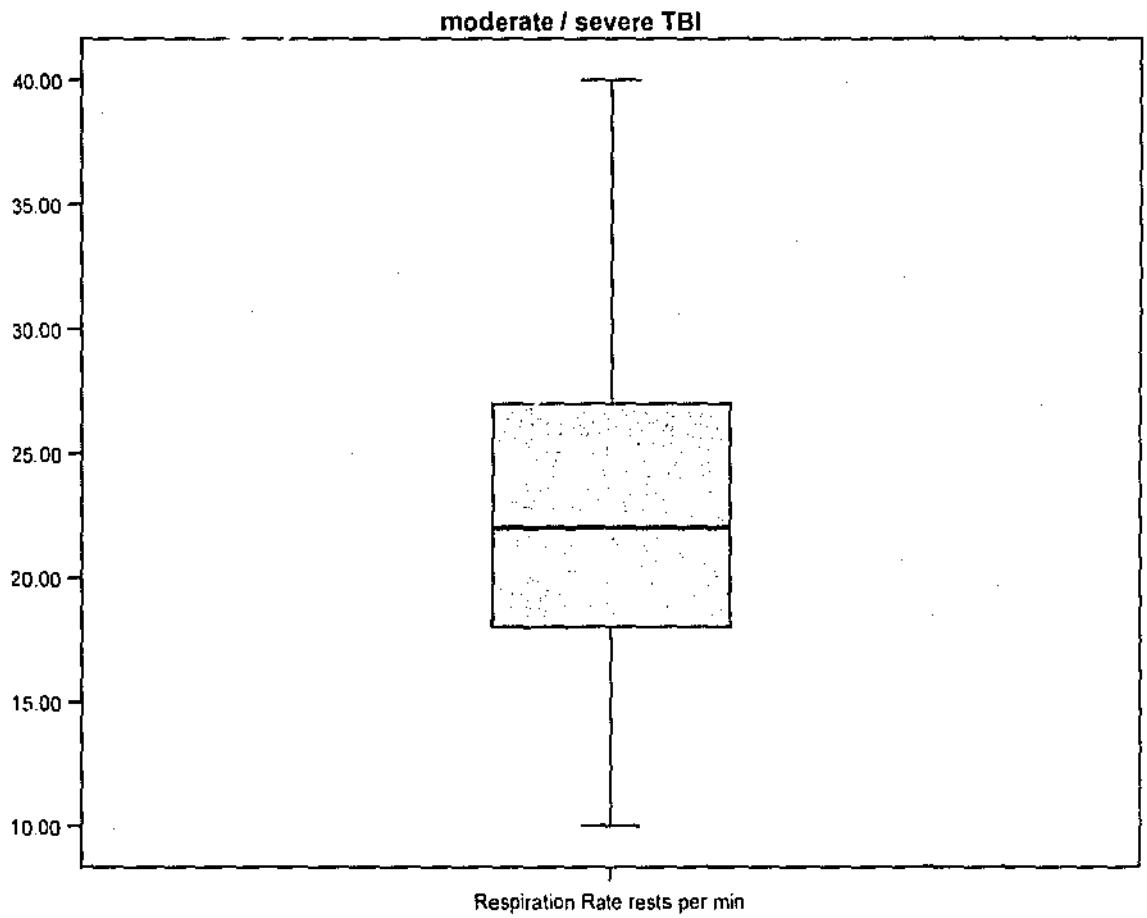
Appendix 27.

Box plot demonstrates normality for Respiration Rate in mild TBI cases



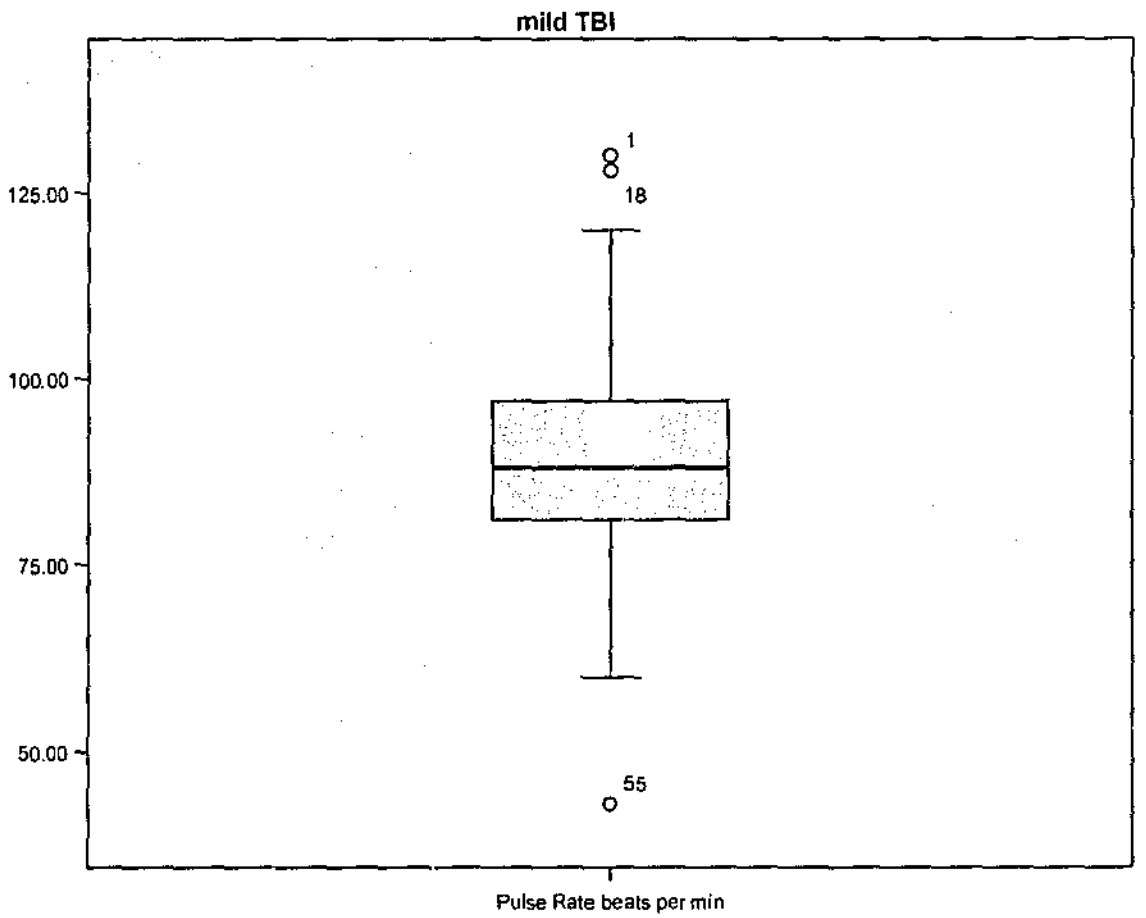
Appendix 28.

Box plot demonstrates normality for Respiration Rate in moderate/severe TBI cases



Appendix 29.

Box plot demonstrates normality for Pulse Rate in mild TBI cases



Appendix 30.

Box plot demonstrates normality for Pulse Rate in moderate/severe TBI cases