Sedative and Analgesic Effects Of Detomidine Or Detomidine and Butorphanol In The Donkey

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Summary

Sedative and Analgesic Effects Of Detomidine Or Detomidine And Butorphanol In The Donkey

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There are approximately forty two million donkeys in the world. All developing countries have an expanding population of donkeys, which are used for the provision of various services. The most commonly performed procedures in donkeys are castrations, tumour removals, foot care and dental treatments. All of these procedures can be performed in standing donkeys provided sufficient analgesia and sedation are provided. The donkey should be recognised and treated in its own light.

Very few analgesics relieve pain without producing side effects. The ideal analgesic would provide good analgesia and sedation without any side effects. Combined with sedation, analgesia aids in the handling of animals and reduces the danger to attendants. Neuroleptanalgesia provides a more potent sedative and analgesic allowing more procedures to be performed. A marked synergistic effect between opioids and alpha$_2$ adrenergic agonists is reported. Detomidine-butorphanol is used extensively for equine sedation and analgesia in the United States of America and Europe.

Currently there is limited information available on effective sedative and analgesic drugs or drug combinations in donkeys. Detomidine and xylazine, which belong to the alpha$_2$ adrenergic agonist group, have been described for use in donkeys. No information exists on the use of opioid drugs or opioid-sedative combinations in donkeys.

Detomidine produces sedation and analgesia of a greater magnitude and a longer duration than xylazine. Detomidine has been used to sedate horses for diagnostic, therapeutic or minor surgical procedures and as part of a premedication or an intravenous anaesthetic protocol. Detomidine is a good analgesic. The duration of sedation and analgesia is dose dependent.

The sedation produced by detomidine alone is not always satisfactory and some horses will respond to noxious stimuli with well-directed kicks. For this reason, detomidine and butorphanol are very often combined. Butorphanol is a synthetic mixed agonist-antagonist opioid. The detomidine is given five minutes before the administration of butorphanol or the butorphanol can follow the detomidine. Sedation is easily extended by additional doses of detomidine and/or butorphanol. This combination produces profound sedation in which horses are apparently unaffected by sounds, tactile stimuli and surrounding activity.

It has been suggested that donkeys require a higher dose of detomidine for sedation than horses. The recommended dose for donkeys is 20-40 μg/kg. The degree and length of analgesia and sedation is dose dependent. A dose of 5-10 μg/kg was found effective for sedation and a dose of 20 μg/kg was effective for sedation and analgesia. No recommended doses for butorphanol in donkeys exist.

Twelve healthy male donkeys were randomly divided into two groups. One group received 10 μg/kg of detomidine while the other group received 10 μg/kg of detomidine and 25 μg/kg of

butorphanol. Sedation was evaluated by a scoring system and characterised by lowering of the head, relaxation of the upper eyelids, drooping of the lower lip and dropping of the ears. Analgesia was evaluated by means of a pinprick method.

The average dose for detomidine was 11.24 μg/kg and that of butorphanol was 28.0 μg/kg. The onset time to sedation was 4 minutes 21 seconds with detomidine alone and 3 minutes 28 seconds with the combination. The average length of sedation for the detomidine group was 20 minutes, and for the detomidine-butorphanol group was 1 hour and 7 minutes. The analgesia lasted twice as long in combination group compared to the detomidine group. Detomidine did not eliminate coronary band pain.

Heart rates dropped significantly in the first minute after the injection in both groups, and this was statistically significant. There was however no statistical difference between the two groups. An atrioventricular and a sinoatrial block were recorded during this trial. The respiratory rates tended to decrease in the first few minutes after which the rate stabilised. Four donkeys receiving butorphanol had Cheyne-Stokes respiratory patterns.

It was evident that the combination of detomidine and butorphanol produced a greater sedative and analgesic effect than detomidine alone. The superior sedation is the result of synergistic effects between detomidine and butorphanol.

This trial has shown that detomidine in combination with butorphanol in donkeys produces sedation that is superior to detomidine on its own and last at least twice as long. Analgesia was dramatically improved with the combination as compared to detomidine alone.

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Chapter 1

Introduction

The donkey has provided service to humanity for hundreds of years and yet little attempt to study any aspect of this equid has occurred in the past. Due to a lack of adequate information for effective veterinary management of this equine, it is treated either on basic medical principles or on the assumption that it is just a small horse. The donkey should be recognised and treated in its own right.

There are approximately forty two million donkeys in the world[18]. Forty million donkeys are found in developing countries, with twelve million in Africa alone[18]. All developing countries have an expanding population of donkeys, which they use for provision of various services. In the course of their use, donkeys suffer from various ailments, which need to be treated. The most commonly performed procedures in donkeys are castrations, tumour removals, foot care and dental treatments[29]. All of these procedures can be performed in standing donkeys provided sufficient analgesia and sedation is provided.

Several analgesics have been used in equine medicine to date. Very few of them relieve pain without producing side effects. The ideal analgesic would provide good analgesia and sedation without any side effects. Relief of pain is essential for humane purposes, to minimise further tissue damage and to prevent self-inflicted injury. Combined with sedation, analgesia aids in the handling of animals and reduces the danger to attendants. Agents from several different pharmacological groups have been used. Opioids, alpha$_2$ adrenergic agonists, non-steroidal anti-inflammatory drugs, local anaesthetics, phenothiazines, benzodiazepines and butyrophenones have been utilised alone or in combination in the effort to find a perfect sedative-analgesic combination. When compared, xylazine is more expensive than detomidine on an equipotent dose basis. Neuroleptanalgesia provides a more potent sedative and analgesic action allowing more procedures to be performed without general anaesthesia. Detomidine in combination with butorphanol has been used extensively for equine sedation and analgesia in the United States of America and Europe. Butorphanol is not currently freely available in the Republic of South Africa.

Very often in field conditions, the availability of anaesthetic equipment is limited and no provision is made for the administration of lengthy general anaesthesia. Equines under go laprascopic and surgical procedures without fluid administration on a regular basis[25]. Under these conditions, the use of drugs that produce minimal side effects are important. It was the aim of this project to determine the effectiveness of a combination of detomidine and butorphanol as an analgesic and sedative in donkeys under field conditions. It also partially addressed the cardiovascular and respiratory side effects, in order to determine the safety of this drug combination in field conditions. It did not attempt to address all the problems that have been noted in the past with detomidine and butorphanol.

Chapter 2

Literature Review

Alpha$_2$ Adrenergic Agonists

Ahlquist initially classified adrenoreceptors in 1948 into alpha and beta sub types[1]. This was based on a series of observations made with synthetic and natural adrenoreceptor agonists on isolated tissues[1]. Smooth muscle, uterine muscle and the vas deferens were used[1]. Noradrenaline and alpha-methyl-noradrenaline induced contraction while adrenaline, isoprenaline and alpha-methyl-adrenaline induced relaxation of these tissues[1]. Ahlquist suggested that two separate populations of receptors caused these opposing responses[1]. Lands in 1967 subdivided the beta adrenoreceptors into subtype beta$_1$ and beta$_2$[35]. In this case the effect of bronchodilation, vasodepression and cardiac stimulation were used. Alpha adrenoreceptors were initially classified on anatomical grounds when neural alpha adrenoreceptors were demonstrated[35]. Anatomical division alone was no longer sufficient and a number of agonists and antagonists were developed to differentiate between prejunctional alpha$_2$ and postjunctional alpha$_1$ adrenoreceptors. At present, the division is made based on the receptor's sensitivity to specific agonists and antagonists[17] (Table 1). Specificity for alpha adrenoreceptors are not absolute and when doses increase other effects may be seen due to binding at other alpha adrenoreceptor sites.

Table 1: Alpha Adrenoreceptors and their agonists and antagonists[17].

Receptor Type	Agonist	Antagonist
Alpha$_1$ & Alpha$_2$	Adrenaline	Tolazoline
	Noradrenaline	Phentolamine
Alpha$_1$	Phenylephrine	Prazosin
	Methoxamine	Corynanthine
Alpha$_2$	Clonidine	Yohimbine
	Xylazine	Idazoxan
	Detomidine	Atipamezole
	Medetomidine	
	Romifidine	

Alpha$_2$ adrenergic agonists decrease sympathetic outflow as one of their primary effects[34]. In many tissues, they inhibit the release of neurotransmitters but in the vascular beds, they cause vasoconstriction[34]. The electrophysiological effects include inhibition of voltage sensitive Ca^{++} channels, acceleration of Na^+/H^+ exchange, opening of K^+ channels and modulation of phosphatidyl inositol turnover[34 50 60]. This leads to hyperpolarisation of the excitable membranes[34]. Many of the effects of alpha$_2$ adrenergic agonists are mediated through G proteins causing changes in cellular adenylate cyclase activity[34 50 60].

Alpha$_2$ adrenergic receptors have now been divided into two subgroups, namely α_{2a} and α_{2b}[50]. Certain subtypes appear to be localised within the brain. In the cerebral cortex and cerebellum, only α_{2a} receptors have been identified while the caudate nuclei contain both subtypes[50]. Three different alpha$_2$ receptor subtypes have been identified, α_2C2, α_2C4 and α_2C10[34 60]. Molecular cloning techniques have shown that several other alpha$_2$-isoreceptors exists, and recently a fourth subtype has been identified[50 60]. The affinity of detomidine, medetomidine and xylazine for the four different alpha$_2$ adrenergic receptor subtypes is equal[53]. These developments may change our current concepts in adrenergic pharmacology.

The alpha$_2$ adrenergic agonists currently used in veterinary medicine include xylazine, detomidine, medetomidine and romifidine. The difference between agonists lies in their

specificity for α_2 and α_1 receptors[34]. Medetomidine has the highest specificity for α_2 receptors and is a complete agonist at these receptors[34]. The d-enantiomer of medetomidine is 4000 times more active than the l-isomer[34].

Sedation and Analgesia

Alpha$_2$ adrenergic agonists are primarily used in veterinary medicine for sedation and analgesia. The sedative action of alpha$_2$ agonists appears to be due to depression of the locus coeruleus in the pons and inhibition of the arousal center[17 34]. Stimulation of central presynaptic alpha$_2$ adrenergic receptors depresses the release of noradrenaline[11 34]. Postsynaptic alpha$_2$ adrenergic receptors are now known to occur in the central nervous system where they are responsible for sedation and the anaesthetic sparing properties of alpha$_2$ adrenergic agonists[61]. The alpha$_2$ adrenergic agonists affect the thalamus and results in spike and wave potentials[34]. This effect may result in some of the analgesia observed with these drugs[34]. Part of the sedation of alpha$_2$ adrenergic agonists are related to noradrenergic neurons in the locus coeruleus[54]. The locus coeruleus projects to the forebrain probably modulating cortical and limbic activity[54]. Destruction of the locus coeruleus does not affect vigilance, and other mechanisms may be involved[54]. Low doses of alpha$_2$ adrenergic drugs have anxiolytic properties similar to the benzodiazepines[61]. These anxiolytic properties are mediated through similar serotonergic pathways[61]. Higher doses of alpha$_2$ adrenergic agonists may produce anaesthesia[34]. The effect is mediated through hyperpolarisation of neuronal cells[34]. Partial and less selective alpha$_2$ adrenergic agonists are not able to reach this anaesthetic effect[34]. All alpha$_2$ adrenergic agonists reduce the requirement for anaesthesia and allow for the smooth induction of anaesthesia[17 34 61].

The sedative effects of alpha$_2$ adrenergic agonists follow a similar pattern regardless of the agent used. The changes seen in the horse are as follows: initial apprehension followed by lowering of the head, drooping of the eyelids and lower lip[17]. The horse then becomes rapidly ataxic[17]. Alpha$_2$ adrenergic agonists require a quiet environment without any stimulation for it to achieve its full effect[57]. It is interesting to note that clonidine has a ceiling effect after which reverses itself[61].

Alpha$_2$ adrenergic agonists have been shown excellent analgesics[17 54]. The analgesia is mediated through spinal and central alpha$_2$ receptors. Higher doses are required for analgesia than what are required for sedation. Visual stimuli are inhibited before auditory stimuli and visceral stimuli before superficial touch[34]. Clonidine, xylazine, detomidine and medetomidine have been administered epidurally to control pain[34]. A marked synergistic effect between opioids and alpha$_2$ adrenergic agonists has been reported[17]. Alpha$_2$ adrenergic agonists induce centrally mediated muscle relaxation[17].

Cardiovascular Effects

Alpha$_2$ adrenergic agonists result in bradycardia even at low doses[17]. Heart rate rapidly declines initially within the first minute. An atrioventricular or sinoatrial block often accompanies the bradycardia[17]. The bradycardia may be mediated through an increase in parasympathetic and a decrease in sympathetic tone over the heart[33 34 45]. Atropine does not totally prevent bradycardia[33]. Heart block is most intense in the first few minutes after administration[17]. A dose dependant trend has also been reported[17]. Considerable debate has occurred over the significance of the heart blocks as second degree atrioventricular and sinoatrial block have been reported in the normal horse[11 12 21 34]. Alpha$_2$ adrenergic agonists produce an initial transient hypertension followed by a mild hypotension[11 12 16 21]. The hypertension occurs very rapidly, usually with in 2 minutes and may last as long as 10 minutes[11 12 16 21]. The hypertension is the result of the direct effects of the alpha$_2$ adrenergic agonists on post synaptic alpha$_1$ receptors[11 16]. Alpha$_2$ adrenergic receptors have also been found extra synaptically in arterial blood vessel walls and result in vasoconstriction[54 61]. Mean

arterial blood pressures as high as 200 mmHg have been reported[16]. The hypertension mediates the bradycardia through baroreceptor activity. The intensity and duration of the hypertension is dose related[17]. Peripheral and central mechanisms are responsible for the hypotension. Hypotension occurs even at low doses of alpha$_2$ adrenergic agonists. No conclusive studies have been done to determine the nature of the hypotension[17]. Cardiac output has been shown to drop by up to 40%[33 37 45]. This occurs very rapidly and slowly returns to normal. The maximal drop in cardiac output coincides with the peak hypertensive effect. The decreased cardiac output is the result of the bradycardia, reduced filling pressure and reduced stroke volume.

Through a reduction in heart rate and contractility, alpha$_2$ adrenergic agonists reduce myocardial energy requirements[38]. Myocardial blood flow is autoregulated, a drop in myocardial energy demand would result in a decrease in coronary blood flow and an increase in coronary vascular resistance with a maintenance of myocardial energy balance[38]. However, alpha$_2$ adrenergic agonists may decrease coronary blood flow on their own causing an imbalance between supply and demand[38].

Alpha$_2$ adrenergic agonists have been shown to alter the distribution of cardiac output[37]. Blood flow is preferentially distributed, with a decrease in blood flow to skin, peripheral shunt flow and spleen[37]. The reduction in blood flow was limited in the heart, brain and kidney[37]. This was accompanied by an increase in mixed venous oxygen extraction while the oxygen uptake remained constant[37]. In all species studied so far, evidence for cardiac hypoxia is weak[34].

Respiratory Effects

There is a lot of debate as to whether alpha$_2$ adrenergic agonists cause respiratory depression[34 36]. Rapid and superficial breathing efforts that gradually change to a deep slow pattern have been reported[17]. Other studies have reported a rapid periodic respiratory pattern[17]. These changes in respiratory pattern are reported in clinical cases[17 45]. Inspiratory noises have been reported. These noises result from obstruction of the upper airways caused by lowering of the head and laryngeal muscle relaxation.

Hypoxaemia following the administration of xylazine has been reported in sheep and cattle[9]. The respiratory effect can be considered with circumspection as several authors have found changes in blood pH and partial pressure of oxygen and carbon dioxide in horses[17 33 45]. These changes have been found small in absolute terms and statistical difference is difficult to achieve[17]. Dose related changes have also been reported[9 17]. The mechanisms by which alpha$_2$ adrenergic agonists bring about hypoxaemia have not yet been elucidated[9]. Current theories have evolved around changes in the cardiovascular system, changes in respiratory pattern, sedation, loss of musculo-skeletal tone and the role of various mediators such as histamines and the cyclo-oxygenase system[9]. Recumbence results in ventilation perfusion changes and a reduction in tidal volume[9]. Recent work has shown a dramatic rise in transpulmonary pressure and this seems to indicate a change in the pulmonary mechanics (non-elastic work of breathing, pulmonary resistance and dynamic lung compliance) [9]. The most likely cause is a pulmonary parenchymal change[9]. Further work has shown that the change in pulmonary parenchyma is the result of peripheral alpha$_2$ receptors[8].

Other Effects

A dose dependant hyperglycaemia has been noted in all alpha$_2$ adrenergic agonists and this is followed by glycosuria. Alpha$_2$ adrenergic agonists produce a diuresis as result of elevated blood glucose levels and inhibition of anti-diuretic hormone[17]. Body temperature generally decreases although high doses of detomidine have been shown to induce hyperthermia[17]. Alpha$_2$ adrenergic agonists may result in the following side effects: priapism, increased uterine pressure, sweating, muscular tremors, increased salivation and reduced gut motility[17].

A major advantage in the use of alpha$_2$ adrenergic agonists is the ability to reverse part or all of the effects of these drugs. There are a number of antagonists available. They are classified as either pharmacological or physiological antagonists. The pharmacological antagonists include yohimbine, tolazoline, piperoxan and idazoxan. The physiological antagonists include 4-aminopyridine, doxapram and caffeine.

Xylazine

Xylazine was developed in early 1960's[60]. Chemically xylazine is known as 2(2,6-dimethyl phenylamine)-4-H-5,6-dihydro-1,3-thiazine[60]. Xylazine is a potent sedative producing drowsiness at low doses (less than 0.5 mg/kg)[57]. Xylazine requires a quiet environment without any stimulation for it to achieve its full effect[57]. As the dose of xylazine is increased the sedation becomes more profound and ataxia of the hind limbs develops[57]. The ataxia may be problematic at high doses and the combination of xylazine with other agents may be useful in reducing the incidence of ataxia[57]. Xylazine is short acting, lasting approximately 20 minutes in the horse[57]. After an intravenous bolus of xylazine a transient hypertension has been noted followed by a longer lasting hypotension[31 57]. The direct action of xylazine on peripheral alpha$_1$ adrenoreceptors results in the initial hypertension[31 57]. The hypotension following the hypertension is centrally mediated through the effects of central alpha$_2$ adrenoreceptors. Second degree atrioventricular block is seen and is presumed to be a physiological response to the hypertension[31 57]. The atrioventricular block is not pathological but disappears when treated with atropine[57]. The cardiovascular side effects are less marked after intramuscular injection[57]. Xylazine is a potent analgesic, of short duration and with no prolonged cardiovascular side effects as is the case with acepromazine[57]. Xylazine has been widely used for its analgesic properties in the treatment of abdominal pain[51]. Respiratory depression is similar to that described for other alpha$_2$ adrenergic agonists[31].

Xylazine has been shown an effective sedative in donkeys[29 39 42]. Higher doses of xylazine have been recommended than what is normally used in equines[29 39 42]. The doses of xylazine normally used are in the range of 0.5 – 2.0 mg/kg[39 42].

Medetomidine

Medetomidine is chemically known as 4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole HCl[60]. Medetomidine has been commonly used in the dog and cat. It is reversed with atipamezole. Medetomidine produces rapid sedation in five to ten minutes after intramuscular injection and within a minute after intravenous injection[55]. It produces rapid and deep sedation lasting 50 minutes in dogs[55]. The cardiovascular response is similar to that described for other alpha$_2$ adrenergic agonists[55]. Arterial blood gas parameters remained adequate while breathing room air, however PaO_2 did decrease to the low normal range[49 55]. Medetomidine in combination with dobutamine and isoproterenol did not alter sedation but did increase heart rates[55]. Dobutamine increased blood pressure while isoproterenol decreased diastolic blood pressure[55]. Medetomidine decreased cerebral blood flow within a minute of administering the drug[55]. The values began to recover within five minutes[55]. Dobutamine did improve cerebral blood flow while isoproterenol significantly increased cerebral blood flow[55]. A dramatic reduction in anaesthetic requirements are evident when medetomidine is used as a premedication before anaesthesia[55].

Medetomidine in horses produced greater ataxia than xylazine[7].

Detomidine

Detomidine is chemically known as (4-(2,3-dimethylphenyl)ethyl)-1H-imidazole HCl[60]. Detomidine is a newer alpha$_2$ adrenoreceptors agonist than xylazine. Detomidine has greater specificity at central alpha$_2$-adrenoreceptors although very high concentrations will activate

alpha$_1$-adrenoreceptors[21]. Detomidine has similar effects to xylazine but detomidine produces sedation and analgesia of a greater magnitude and a longer duration than xylazine[12 57]. Sedative effects become apparent within two to five minutes after intravenous injection[11]. Detomidine has been used to sedate horses for diagnostic, therapeutic or minor surgical procedures or as part of premedication or intravenous anaesthesia[11 12]. The duration of sedation is dose dependent with larger doses producing longer duration of sedation[11 12]. Detomidine has been administered intramuscular or intravenously to horses at doses ranging from 5–40 μg/kg[11 12]. A dose of 10-20 μg/kg is an effective sedative and analgesic[11]. For the induction of general anaesthesia, detomidine has been combined with ketamine, tiletamine-zolazepam, guaifenesin and thiobarbiturates[12]. Detomidine may reduce the anaesthetic requirements by up to 55%[12 56]. An increase in dose results in progressive ataxia[11 12 16 17 57]. High doses of detomidine result in swaying of the animal on its feet, which can result in the animal falling[11]. The sedation produced by detomidine is not always satisfactory and some horses will respond to noxious stimuli with well-directed kicks[10 11 12 16 17 57].

The analgesic effects of detomidine have been used to good advantage in horses with severe abdominal pain[12 27]. Excellent sedation and analgesia are provided, allowing for examination of difficult to manage horses. No study has been undertaken to evaluate the cardiovascular side effects of detomidine in shocked horses[12]. At low doses, the analgesic effect is poor[11].

Cardiovascular and Respiratory Effects

After intravenous injection there is a dose dependant rise in blood pressure and systemic vascular resistance, usually with in two to five minutes accompanied by a significant fall in heart rate[10 11 12 56 57]. The bradycardia is variable in duration and degree[11]. After the hypertension, systemic vascular resistance drops[56]. This is followed by a more prolonged mild hypotension[10 11 12]. Left ventricular stroke work index increases and systemic vascular resistance decreases[56]. The rate pressure product indicates that detomidine is safe for left heart function[56]. The heart rate usually returns to normal within a few minutes of administration[12 57]. The bradycardia and hypotension are dose dependent and reach their maximum effect 15 to 30 minutes after intravenous injection[12]. Central venous pressure and pulmonary capillary wedge pressure are not altered by detomidine in horses[56]. After a continuous infusion, heart rate was higher and cardiac index lower than when compared to a bolus dose[14]. Systemic vascular resistance was 50% higher in the infusion group[14]. There is evidence to suggest that cardiovascular responses to detomidine may be related to plasma concentrations[14].

Atrioventricular and sinoatrial heart blocks have been recorded[10 11 12]. Cardiac output and tissue perfusion are reduced as a result of the drop in heart rate, although no clinical problem have been reported as a result of low tissue perfusion[11 12 43 56]. The muscle microcirculation remained stable; suggesting that detomidine does not alter autoregulation[56]. Oxygen transport is reduced due to the reduction in cardiac output[56]. The elevated oxygen consumption and reduced oxygen transport may reduce the margin of safety of this drug during anaesthesia especially within 20 minutes after administration[56].

Relaxation of the laryngeal and nasal alar muscles predisposes horses to upper airway obstruction and stridor[12]. Respiratory rate is reduced but arterial carbon dioxide levels do not increase significantly[12]. Arterial partial pressure of oxygen is reduced[12]. This reduction has not been associated with any clinical symptoms but arterial hypoxaemia is possible[12].

Other Effects

Other side effects noted with detomidine are diuresis, piloerection, penile protrusion, sweating, hyperglycaemia and respiratory changes[11 12 16]. The diuresis is associated with increased glomerular filtration rates, inhibition of anti-diuretic hormone release, inhibition of

anti-diuretic hormone effect on the renal tubules and increased release of atrial natriuretic factor[12 16]. The administration of detomidine during pregnancy may be associated with abortions[12]. Detomidine increases gut motility of the proximal gastrointestinal tract in a dose dependant manner while reducing caecal and colonic motility[12].

Detomidine has been used safely in the epidural and subarachnoid spaces[12].

Detomidine in Donkeys

The use of detomidine in donkeys is not very well described in the literature. Sedation in donkeys usually occurs within two to three minutes after intravenous administration[43]. It has been suggested that donkeys require a higher dose of detomidine for sedation than horses. The recommended dose for donkeys is 20-40 μg/kg[21 62]. The analgesic and sedative duration is reviewed in Table 2. The degree and length of analgesia and sedation are dose dependent[43]. A dose of 5-10 μg/kg was found effective for sedation and a dose of 20 μg/kg was effective for sedation and analgesia[43]. Bradycardia was variable in degree and duration, and dependent on dose[43]. Cardiovascular abnormalities were transient, none were recorded after 40 minutes and they were not considered dangerous[43]. No significant changes to haematological and biochemical parameters were found[43].

Table 2: Analgesic and sedative effects of detomidine in donkeys[43].

Dose	Duration of Sedation	Duration of Analgesia	Recovery Time
5 μg/kg	21 +/- 1.67 min	No analgesia	33 +/- 2.29 min
10 μg/kg	35 +/- 4.01 min	No analgesia	55 +/- 3.17 min
20 μg/kg	75 +/- 3.75 min	52 +/- 4.16 min	86 +/- 3.56 min
40 μg/kg	95 +/- 6.01 min	80 +/- 3.17 min	139 +/- 9.86 min

Romifidine

Romifidine produces dose dependant sedation in horses[16]. The sedative effects last longer than detomidine or xylazine but it is less potent than either of these drugs[16]. Romifidine produces a more significant bradycardia[16]. Romifidine produces less ataxia than detomidine or xylazine[16].

Opioids

An opioid by definition is a substance with morphine like action. In the body, enkephalins, endorphins and dynorphins are naturally occurring opioids.

Opioids have traditionally been used as analgesics. In general opioids produce very little sedation when used on their own but when opioids are combined with sedatives and tranquillisers, excellent results can be achieved[57]. Stimulation of mu-receptors results in analgesia, sedation, hypothermia, miosis, bradycardia, euphoria and cardiovascular and respiratory depression while the sigma receptors cause indifference, delirium, ataxia, tachycardia and mydriasis[15 44]. The mu_2-receptors are more responsible for respiratory depression while the mu_1-receptor causes supraspinal analgesia and euphoria[15 40]. Kappa receptors are responsible for spinal analgesia, sedation, physical dependence and reverse respiratory depression[15 40]. Opioids demonstrate different affinities for opioid receptors. Mixed agonist-antagonists and partial agonists have different affinities for opioid receptors leading to complex pharmacological effects[44].

Cardiovascular and Respiratory Effects

The cardiopulmonary effects of opioids are dependent on the species, drug dose, concurrent drug administration and the status of the central nervous system at the time of administration[52]. Hypotension associated with hypovolaemia and increased venous

capacitance has been reported with the administration of opioids. Hypotension, puritis and urticaria have been described due to the release of histamine[15]. Opioids alter vagal tone and result in bradycardia, sinoatrial or atrioventricular heart block[15].

Severe respiratory depression is a common side effect seen in man[15]. In horses, respiratory depression does not appear to be problematic when used at therapeutic doses[10 57]. Opioid induced respiratory depression is mediated through depression of the bulbar and pontine nuclei of the brain stem[15]. Patients become more dependent on the hypoxic drive for control of ventilation[15]. Tidal volume, respiratory rate and minute ventilation are reduced by opioids[15]. Opioids may induce a Cheyne-Stokes breathing pattern[15].

Other Effects

Gastrointestinal motility is reduced and oesophageal tone lowered by opioids[15 57]. The tone in the gastric antrum and the first part of the duodenum is increased[15]. Ileus is the result of neurogenic inhibition mediated by non-cholinergic, non-adrenergic vagal inhibition of the stomach and sympathetic inhibition through the rest of the gastro-intestinal tract[15]. Gastric, biliary and pancreatic secretion is inhibited[15]. An increase in tone of the urinary sphincter and central inhibition of the detrusor muscle results in urinary retention[15].

Excitation is another common side effect especially with morphine and pethidine[10 57]. Excitation is an easily rectified side effect of opioids and as such is not a contraindication[57]. Nausea and vomiting may occur due to direct stimulation of the chemo-emetic trigger zone[15]. Muscle rigidity is well described in man and is centrally mediated[15]. Opioids are addictive in man[15]. This has resulted in stringent control and legislative requirements. Newer synthetic opioids, especially those with agonist and antagonist properties, are less addictive and are therefore less stringently controlled. Antagonists such as nalorphine, levallorphan and naloxone can reverse the effects of opioids.

Morphine may cause hypertension and a marked bradycardia in the horse[10 31]. The morphine hypertension can be as great as that caused by detomidine[10]. The hypertension is the result of a centrally mediated increase in peripheral vascular resistance[44]. Methadone has minimal cardiovascular side effects on its own[10]. Normally opioids are used in very low doses for chemical restraint of horses and thus the side effects are reduced. Methadone and butorphanol are capable of causing ataxia[10].

Butorphanol

Butorphanol is a synthetic mixed agonist-antagonist opioid and as such has a ceiling effect[36 51 58]. Butorphanol has been recommended as a sedative, analgesic, antitussive and adjunct to general anaethesia[44 51]. It is approximately 7, 20 and 40 times more potent than morphine, pentazocine and meperidine as an analgesic[44 51]. At a dose of 0.4 mg/kg, butorphanol is capable of relieving superficial pain for 30 minutes and visceral pain for 90 minutes[31 44]. Butorphanol is less effective in increasing visceral pain threshold than xylazine but more effective than morphine, levorphanol and flunixin[31]. A dose of less than 0.05 mg/kg resulted in poor superficial analgesia but effective visceral analgesia[30]. The analgesic effect, duration and depth are dose related[30]. Doses of more than 0.22 mg/kg intravenously are associated with excitation, ataxia and muscle twitches while doses of 0.1 mg/kg are associated with minimal effects[44 51 52]. High doses of butorphanol will result in an antagonising effect with reversal of analgesia[40]. Cardiopulmonary effects are minimal when administered in analgesic doses although butorphanol may induce a tachycardia[31 44 52]. These minimal cardiovascular effects are echoed in studies done in human beings and dogs[10 52]. Butorphanol is a potential respiratory depressant but the observed changes in partial pressure of oxygen and carbon dioxide are not statistically significant[31 51 52 58]. The cardiovascular and respiratory abnormalities are more prominent in pain-free animals[51].

Neuroleptanalgesia

Laborit, in 1949, introduced the concept of anaesthesia that blocked the cerebral cortical, cellular, endocrine and autonomic responses to surgery[3]. This state was known as "ganglioplegia" or "neuroplegia" and was achieved with a cocktail of chlorpromazine, promethazine and meperidine[3]. In 1959, De Castro used this idea to derive the concept of neuroleptanalgesia[3]. Neuroleptanalgesia can be described as a detached, pain free state of immobility and insensitivity to pain[3]. The clinical characteristics are analgesia, absence of apparent motor function, suppression of autonomic reflexes, maintenance of cardiovascular stability and amnesia[3].

The combinations of tranquillisers, sedatives and opioids produce far better sedation than the drugs used alone[10 58]. This is a result of the interaction called synergism[10]. The dose of each agent is also reduced[10]. Acetylpromazine and xylazine in combination with various opioids have been used to sedate horses[57]. The opioids used have included morphine, pethidine, methadone, pentazocine, buprenorphine and butorphanol[10 12 17 57] (Table 3). Maximum sedation usually appears within 5 to 15 minutes after injection of the opioid. The sedation is maintained for at least 45 minutes[10]. Signs of mild excitation seen after injection of opioids are muscular twitches, head jerks, muzzle tremors, head pressing and raised tails[10]. These effects usually occur shortly after the administration of the opioid but may continue for as long as 30 minutes after administration[10]. Opioids are capable of producing a heart block[10]. Following a combination of detomidine and opioids, the animal stands rigidly on all four legs. It has been noted with detomidine that the animal will stagger and then regain their balance. With the combination of detomidine and butorphanol, animals appear to be less aware where their feet are[10]. This situation can be serious if the animals are already very ataxic after the administration of the sedative[10].

A combination of detomidine-morphine may result in a transient tachycardia. Following the administration of morphine, the tachycardia was accompanied by a rise in mean arterial blood pressure[10]. The cardiovascular effects are similar with pethidine but are less marked while methadone causes little effect[10]. Morphine causes a rise in arterial partial pressure of carbon dioxide and a reduction in partial pressure of oxygen[10]. The effect of pethidine on carbon dioxide is transient[10].

Xylazine as a Neuroleptanalgesic

Xylazine has been used in combination with fentanyl, meperidine, methadone, oxymorphone, morphine and pentazocine[51]. The sedative and analgesic effects of these combinations are superior to that of xylazine alone[51]. The combination of morphine with xylazine has been shown to provide deep sedation and profound analgesia when given in combination. One of the major side effects has been emergent excitement. This is due to the long half-life of morphine in comparison to xylazine. Excitement is seen when the morphine is given before the xylazine has had a chance to exert its effects. An additional dose of xylazine or acetylpromazine is given to avoid the excitement phase[57]. The mixed agonist-antagonist opioids did produce emergent excitement[57] and cardiovascular and respiratory stability was good[57].

Initially xylazine was given intravenously followed by butorphanol 6 minutes later[51]. The xylazine produced cardiovascular depression, which had returned to normal 15 minutes after the administration of butorphanol[51]. Within 5 minutes of the administration of butorphanol, the horses failed to react to the application of towel clamps and a skin incision, however they had reacted when only xylazine was used[51]. The analgesia lasted for 30 minutes, which was sufficient time for incision through the abdominal wall and closure of the wound[51]. The cardiovascular and respiratory abnormalities are not statistically significant and are only transient[51]. The addition of butorphanol to xylazine did not increase the degree of ataxia[51].

Table 3: Neuroleptanalgesic combinations11 [57].

Drug Combination	Doses	Notes
Acetylpromazine Pethidine	0.04 mg/kg 0.6 mg/kg	Sedation is similar to xylazine with less ataxia.
Acetylpromazine Pethidine Xylazine	0.04 – 0.06 mg/kg 0.3 – 0.4 mg/kg 0.2 mg/kg	Cardiovascular & respiratory effects poor documented. Deep sedation for 20 – 30 minutes.
Acetylpromazine Methadone	0.05 – 0.1 mg/kg 0.1 mg/kg	Fewer side effects reported than combinations with pethidine.
Xylazine Methadone	0.5 – 1.0 mg/kg 0.1 mg/kg	Cardiovascular stable. No response to auditory stimulus.
Acetylpromazine Xylazine Methadone	0.04 – 0.06 mg/kg 0.2 mg/kg 0.06 mg/kg	Not well documented. Used practically due to superiority of methadone over pethidine.
Xylazine Morphine	1.0 mg/kg up to 0.75 mg/kg	Produces profound sedation. Excitement due to morphine.
Xylazine Pentazocine	1.0 mg/kg 0.3 – 0.6 mg/kg	Used clinically. Not well documented.
Acetylpromazine Pentazocine	0.05 mg/kg 1.0 mg/kg	Not well documented. Clinical use limited.
Acetylpromazine Buprenorphine	0.05 mg/kg 0.01 mg/kg	No significant cardiovascular and respiratory side effects.
Xylazine Buprenorphine	0.5 – 1.0 mg/kg 0.01 mg/kg	Analgesia and sedation excellent. No emergence excitement.
Detomidine Morphine	0.01 mg/kg 0.1 mg/kg	Marked cardiopulmonary effects.
Detomidine Methadone	0.01 mg/kg 0.1 mg/kg	Incompletely abolished responses to stimuli.
Detomidine Pethidine	0.01 mg/kg 1.0 mg/kg	Apparent sedation did not increase, excitement and ataxic.
Detomidine Butorphanol	0.01 mg/kg 0.05 mg/kg	Abolished response to most stimuli.

Detomidine-Butorphanol

Because horses are still capable of responding when only alpha$_2$ adrenergic agonists are used, detomidine is very often combined with opioids[10 11 12 17 51]. Butorphanol and detomidine is an effective combination especially when detomidine alone has failed[10 11 17]. This combination is undoubtedly synergistic[58]. A dose of 10 μg/kg of detomidine in combination with 25 to 50 μg/kg of butorphanol was used[10 36 58]. The detomidine is given five minutes before the administration of butorphanol[10] or the butorphanol can follow immediately after the detomidine[58]. Sedation is easily extended by additional doses of detomidine and/or butorphanol[58]. Excitation shortly after administration has been noted[10]. The blood pressure effects of this combination are similar to detomidine[10]. Heart rates drop dramatically after the administration of this combination of drugs[58]. This is more than likely due to the detomidine component. Butorphanol did not alter the arterial partial pressure of carbon dioxide and oxygen significantly[10 36]. Ataxia is not severe but is dependent on the dose of detomidine given[10 58]. The ataxia is a potential danger, but most horses appear to "wake up" and correct their balance before becoming sedated again[58]. Relaxation of the penis does occur and may be useful in the examination of the penis[58]. Sweating has not been found a problem with the combination as it is with detomidine alone[58].

This combination produces profound sedation in which horses are apparently unaffected by sound, tactile stimuli and surrounding activity[58].

Romifidine is the latest alpha$_2$ adrenergic agonist to be developed and has already been used successfully in combination with butorphanol[6].

Chapter 3

Published Journal Article

The Sedative and analgesic effects of detomidine-butorphanol and detomidine alone in donkeys.

Joubert KE, Briggs P, Gerber D, Gottshalk RG

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Book review — Boekresensie

A quantitative biology of the pig

Edited by I Kyriazakis

1999. CABI Publishing, Wallingford, UK, 398 pp., 62 figures, 52 tables. Price £60.00. ISBN 0 85 199 273 0.

The measurability of pigs is not a new concept, but this book adds depth and brings much of new investigative techniques to the questions of pig biology. The overall intention is to improve simulation modelling as an eventual production tool. The editor states, in the final chapter, that there are problems involved in converting models into practice and difficulties in including stochastic elements when trying to predict population performance from quantitative measurements in individual animals. This does not detract from the wealth of usable information in this excellent book.

The editor has enlisted some 30 contributors from outstanding scientific teams worldwide. In the course of the 16 chapters, most aspects of the pig, its composition, reaction to environment, social interaction, breeding patterns, pre- and post-natal growth, sow lactation, lean and fat development, hormone controls and other factors are examined, quantified and presented in readable form, aided by numerous tables, graphs and diagrams.

The major area of investigation is, understandably, nutrition. Nearly half of the book is devoted to detailed examination of this subject, from constituents of feeds and their absorbability and metabolism to the requirements of pigs at all ages and in various circumstances.

The contributors take a new and critical look at many conventional wisdoms – are we really able to analyse amino acids, is sow milk the best food for piglets, why do we use 6.25 to convert N to CP, why do we have problems balancing the energy flow equation, should we not be more concerned with physical and physiological attributes of feeds than chemical analysis ...?

Although this book is written largely for nutritionists, animal scientists and statisticians, every chapter has a final discussion or conclusion paragraph that summarises the content, and the references are numerous and recent.

Any veterinarian who is concerned with modern pig production will find a great deal of up-to-date, authentic and useful information in its pages.

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Article — Artikel

The sedative and analgesic effects of detomidine-butorphanol and detomidine alone in donkeys

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ABSTRACT

Butorphanol and detomidine constitute an effective combination for sedation and analgesia in horses. This trial was undertaken to assess the effectiveness of this combination in donkeys. The detomidine and butorphanol were given intravenously one after the other. A dose of 10 μg/kg of detomidine and 25 μg/kg of butorphanol was used. Sedation is easily extended by additional doses of butorphanol. The average dose of detomidine was 11.24 μg/kg and that of butorphanol was 28.0 μg/kg. Four donkeys in the detomidine group required additional sedation and analgesia. Detomidine alone did not totally eliminate coronary band pain. Heart rates dropped significantly in the first minute after the injection of the combination. One donkey developed an atrioventricular block, while another developed a sino-atrial block. Four donkeys developed a Cheyne-Stokes respiratory pattern. The combination of detomidine and butorphanol is an effective combination for sedation and analgesia of donkeys for standing procedures.

Key words: analgesia, butorphanol, detomidine, donkey, neuroleptanalgesia, sedation.

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INTRODUCTION

Forty million donkeys are found in developing countries, with 12 million in Africa alone[8]. Most developing countries have an expanding population of donkeys, which they use for provision of various services, including traction and transportation of people and goods[8]. The most commonly performed surgical procedures in donkeys are castrations, tumour removals, foot disorders and dental treatments[12]. All of these procedures can be performed without general anaesthesia if sufficient analgesia and sedation are provided. The donkey should not be regarded as small horse, but should be recognised and treated as a species in its own right.

Often under field conditions the availability of anaesthetic equipment is limited. No provision is made for the administration of lengthy general anaesthetics. Under field conditions, the use of drugs that produce minimal side-effects becomes important, as the availability of medical care is limited. Few analgesics relieve pain without producing side-effects. The ideal analgesic provides good analgesia and sedation without any side-effects. Combined with sedation, analgesia aids in the handling of animals and reduces the danger to attendants.

Detomidine, (4-(2.3-dimethylphenyl) ethyl)-1H-imidazole HCl[28], is most specific for central alpha$_2$ adrenoreceptors, but high doses will activate alpha$_1$ adrenoreceptors[9]. Although similar to xylazine, detomidine produces sedation and analgesia of greater magnitude and longer duration[4,25]. Sedative effects become apparent within 2–5 minutes[3]. In horses, detomidine has been used for diagnostic, therapeutic or minor surgical procedures, for premedication, or as part of an intravenous anaesthetic[3,4]. The duration of sedation is dose-dependent, with larger doses resulting in a longer duration of action[3,4].

The use of detomidine in donkeys is not well documented[19,29]. Sedation in donkeys usually occurs within 2–3 minutes of intravenous administration[19].

Butorphanol is a synthetic mixed agonist-antagonist opioid and has a ceiling effect on opioid receptors after which antagonism at opioid receptors may occur[16,22,26]. Butorphanol has been recommended as a sedative, analgesic, antitussive and adjunct to general anaesthesia in dogs, cats, horses and laboratory animals[20,22]. To our knowledge the use of butorphanol in donkeys has not been described.

Neuroleptanalgesia provides more potent sedation and analgesia, allowing many procedures to be performed on a standing animal. A combination of tranquillisers, sedatives and opioids produces far better sedation than any of these drugs used alone[2,26] as a result of synergism, and the dose of each individual agent is reduced[2]. Acepromazine and xylazine in combination with various opioids have been used to sedate horses[25]. The opioids used have included morphine, pethidine, methadone, pentazocine, buprenorphine and butorphanol[2,4,7,25]. A marked synergistic effect between opioids and alpha$_2$ adrenergic agonists has been reported[7].

Butorphanol and detomidine have been shown to be an effective combination especially when detomidine alone has failed[2,3,7,26].

The combination of detomidine and butorphanol has not been evaluated in donkeys. In view of the suggestion that higher doses of detomidine are required in donkeys[9,19,29], the potential reduction of the detomidine dose by the addition of butorphanol needs to be examined. It is furthermore proposed that the synergistic effect of detomidine and butorphanol increases the intensity and duration of analgesia.

MATERIALS AND METHODS

Twelve healthy male donkeys between the ages of 6 months and 15 years were used in the trial. These donkeys were part of a trial to evaluate a novel surgical technique for the castration of donkeys laparoscopically. The weight of the animals varied from 90 to 180 kg. Each animal was identified by a freeze-branded number on the withers. The donkeys were randomly assigned to one of 2 groups by drawing lots. Group D donkeys received 10 μg/kg of detomidine (Domosedan, Novartis Animal Health) and Group DB donkeys received 10 μg/kg of detomidine and 25 μg/kg of butorphanol (Turbogesic, Forte Dodge Animal Health) at time 0. Group D had a mean

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age of 2.4 ± 1.4 years and that of group DB was 7.4 ± 6.3 years. The difference in mean ages is the result of group DB including a single donkey aged 13 years. The mean mass of Group D was 144 ± 22.6 kg and that of Group DB was 139 ± 34.6 kg. No statistical difference was found between the ages and weights of the 2 groups using Student's *t*-tests.

The surgeons performing the procedure and selected observers did not know which drug had been administered. All the donkeys were sedated in order to facilitate their castration. Two donkeys were used as part of the pilot trial and were castrated by means of a standard castration procedure as described for equines[27]. These results of the pilot trial were not included for analysis. In the remaining 10 donkeys the testicular artery was ligated laparoscopically with a Filshie clip as described by Briggs, Gottschalk, Gerber and Joubert (Research Protocol, University of Pretoria, Project No. 36.5.95).

Before commencement of the trial, complete physical examination and blood counts were performed to establish clinical normality. Preoperative serum samples were taken and stored for analysis as required. Food was withdrawn from the donkeys 24 h before the trial and *ad lib* water was allowed until the time of the trial. The animals were kept outdoors in paddocks. The preparation involved the following: an area over the left jugular grooves, the left shoulders, sternum and pectoral muscles was shaved. The jugular groove was surgically prepared. A small bleb of local anaesthetic (Lignocaine 2 %, Centaur Laboratories) was placed subcutaneously over the jugular vein and an intravenous Teflon catheter (Intraflo, AME Medical) was inserted into the left jugular vein and sutured in place. This catheter was used for all intravenous drug administrations. The catheter was flushed regularly with heparinised saline to ensure that it remained patent throughout the trial. The donkeys were then led inside and restrained in stocks. Electrocardiograph (ECG) electrodes were placed in a base-apex configuration on the shaved areas of the left shoulder, sternum and pectoral muscles. The ECG electrodes were connected to an ECG monitor (Capnomac II, Datex). The collecting tube from a capnograph (Ultima Capnomac, Datex) was placed into the left ventral meatus.

All data were recorded at the following time intervals: –5, 0, 1, 2, 3, 4, 5, 10, 15, 20 min and then every 10 min thereafter until the procedure was completed, unless specified. Heart rate and rhythm were monitored using the ECG machine. Rhythm abnormalities were recorded in terms of frequency, type and length of time after administration of the drugs. Respiratory rate and rhythm were monitored physically by chest wall movements and on the capnograph to detect apnoeic periods. Respiratory rhythm abnormalities were recorded. Mucous membrane colour and capillary refill times were monitored and abnormal findings were recorded.

Sedation was characterised by lowering of the head, relaxation of the upper eyelids, drooping of the lower lip and dropping of the ears. The sedation was graded according to a numerical scale: 0 = no sedation; 1 = head normal position, relaxed lower lip and eyelids; 2 = head lowered, drooping eyelids and lip; 3 = head fully lowered, drooping eyelids and lips[26]. The time to onset of sedation was recorded.

The degree of analgesia was assessed by the response of the animal to a needle-prick applied to the base of the ear, shoulder and fore hoof coronary band at time 0 and thereafter at 5, 10, 15, 20 min and every 10 min thereafter until the end of the procedure[15,21]. The analgesia was scored according to a numerical rating scale: 0 = no analgesia; 1 = conscious awareness and subdued response; 2 = awareness but no response; 3 = no response to test[2,6,26]. The use of numerical rating scales for the assessment of pain is a useful tool but the sensitivity of this scale in detecting small differences is limited[1].

Additional doses of detomidine and/or butorphanol at 25–50 % of the original dose were given when the degree of sedation or analgesia was considered insufficient. This occurred only in group D. The sedation or analgesia was considered insufficient when the donkeys moved in response to surgical stimuli, were restless in the crush or the sedation or analgesic score was 0–1. Donkeys that received additional doses of either butorphanol or detomidine were given a score of 0 for sedation and analgesia for evaluation purposes from that point onwards.

The time to the end of sedation was recorded. The surgeon performing the procedure and the observers assessed the degree of analgesia and sedation subjectively using the response to surgical stimuli and the ability to complete the procedure with minimum discomfort to the donkey. When additional doses of detomidine and/or butorphanol were required, this was used as the end point of sedation.

Emergency drugs and yohimbine were kept at hand. Animals that developed clinical abnormalities were treated appropriately according to accepted practices. All abnormal clinical findings were noted and treatments given recorded.

Groups were compared according to weight, age, drug dose and procedure time was done using Student's *t*-tests. For sedative and analgesic times a 2-way analysis of variance was used. The statistical difference was set at 0.05. All data from each group were analysed for means, standard deviations and modes. Heart and respiratory rates were analysed within each group and between groups. The data from times –5 and 0 minutes were pooled when analysed with reference time 0. Sedative and analgesic scores were summed separately for each time interval. The summed values were used for analysis and these were graphed. Histograms were also used to determine the frequency of a particular sedative or analgesic score in each of the 2 groups. Graphs were used to show trends (blood pressure, respiratory rate).

The Research and Ethics committees of the Faculty of Veterinary Science at the University of Pretoria approved this trial (Project Number: 36.5.97).

RESULTS

Drug dosages

Initially Group D received 9.9 ± 1.5 μg/kg of detomidine while Group DB received 10.1 ± 4.7 μg/kg of detomidine and 25.2 ± 1.2 μg/kg of butorphanol. There was no statistical difference between the 2 groups with respect to the initial dose of detomidine given ($P > 0.05$). In Group D, 1 donkey received an additional dose of detomidine (3.4 μg/kg), while 2 donkeys received butorphanol at an average dose of 24.3 ± 2.4 μg/kg. Group DB did not receive additional doses of detomidine or butorphanol for analgesia or sedation. Table 1 summarises the dose and drugs given to each donkey.

Sedation and analgesia

Sedation

The onset of sedation (sedative score ≥2) was more rapid in Group DB than in Group D (Table 2), and this was statistically significant ($P < 0.01$). The average length of sedation for Group D was 20 min and that of Group DB was 1 h 7 min (Table 2), which was also statistically significant ($P < 0.01$). A sedative score of 3 was maintained for only 10 min in Group D compared to 40 min in Group DB. Two donkeys in Group D did not achieve a score of 3 while all donkeys in Group DB did. All donkeys in Group D had achieved a score of 1 by 20 min while most of the donkeys in Group DB had a score of 3 for the same time interval. By the end of the procedure, most donkeys

in Group DB had a score of 2, while the Group D donkeys showed no evidence of sedation and had then required additional drugs. Donkeys requiring additional sedation in Group D that were given butorphanol easily obtained a score of 3. In summary, sedation was of shorter duration and intensity in Group D than in Group DB (Fig. 1).

Analgesia

For analgesia tests conducted around the head, Group D produced a mode score of 2 at 5 min, which lasted for 20 min. Group DB produced a mode score of 2 at 5 min and 3 at 10 min. In Group DB a score of 2 or more was maintained for at least 40 min. Similar results were seen for the analgesia tests conduct on the shoulder area. In Group D, coronary band pain was poorly attenuated at all points in time while in Group DB a mode score of 2 was initially achieved. In general, the analgesia lasted twice as long and was of greater intensity in Group DB compared to Group D. The difference between detomidine alone and detomidine-butorphanol are also more apparent graphically as illustrated in Figs 2–4. During the procedure, 3 donkeys from Group D required additional sedation and analgesia, 2 donkeys received butorphanol while 1 donkey received detomidine.

Procedure times

The median times of the procedures performed in Group D and Group DB were of similar length, 45 min 31 sec and 43 min, respectively, and were not statistically different, ($P > 0.05$) (Table 2).

Cardiovascular and respiratory changes

The pre-treatment mean heart rates were 53.3 and 45.3 beats per minute for Group D and Group DB respectively, which dropped to 38.4 and 29.4 in the first minute after treatment for Group D and Group DB. The drop in heart rate was statistically significant and heart rate remained significantly depressed through the entire procedure ($P < 0.05$). There was, however, no statistical difference between the 2 groups at any time. The heart rates are graphically represented in Fig. 5. One donkey in Group D developed an atrioventricular block while another donkey in group DB developed a sino-atrial block.

The respiratory rates tended to decrease in the first few minutes, after which the rate stabilised. There was, however, no statistically significant difference in respiratory rate between the groups. Four donkeys had irregular respiratory patterns.

Table 1: **Drug dosages.**

Group/ Donkey No.	Detomidine 1st dose[a]	Detomidine Additional dose[b]	Butorphanol 1st dose	Butorphanol Additional dose
Group D				
1	1.70			4.00
8	1.40	0.50		
25	1.20			
31	1.20			3.00
20	1.60			
Group DB				
22	1.20		3.00	
11	1.00		2.20	
3	1.80		4.50	
14	1.60		4.00	
9	2.70		6.80	
Mean	1.54	0.50	4.10	3.50
Mean (μg/kg)	10.9	3.4	25.2	12.2

[a]Dosages are recorded in milligrams given to each donkey at time 0 (1st dose) and the dose of any additional drugs given when sedation or analgesia was insufficient.
[b]The time to the administration of any additional drugs is indicated in Table 2 under the heading 'length of sedation'.

Table 2: **Sedation and procedure times** (min:sec).

Group D Donkey No.:	1	8	25	31	20	Mean	SD[a]
Onset of sedation[b]	4:16	4:28	4:50	4:08	4:03	4:21	0:19
Length of sedation[c]	14:20	21:32	21:12	8:52	36:08	20:25	10:14
Length of procedure[d]	57:31	82:00	18:06	21:19	48:40	45:31	26:34
Group DB Donkey No.:	22	11	3	14	9	Mean	SD
Onset of sedation	3:38	3:28	3:28	2:56	3:49	3:28	0:20
Length of sedation	89:16	87:13	59:15	43:54	59:11	67:46	19:44
Length of procedure	42:00	30:12	54:32	39:45	48:30	43:00	9:12

[a]SD is the standard deviation for each measurement.
[b]Onset of sedation records the time from drug administration to the point when a sedation of score of 2 or more was achieved.
[c]Length of sedation gives the time from drug administration until a sedative or analgesic score of less then 2 was achieved.
[d]Length of procedure records the duration of the laparoscopic procedure until the last stitch was placed.

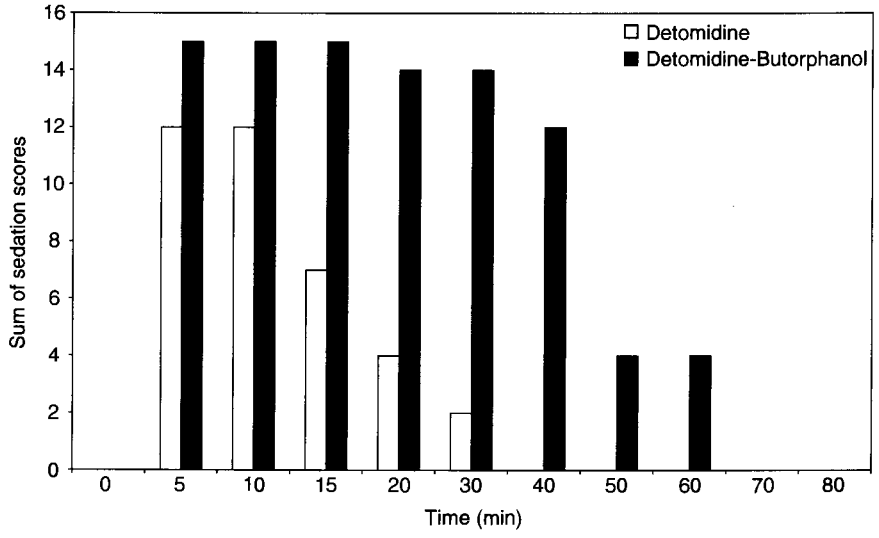

Fig. 1: **Sedation score per time interval. The scores for each group were summed. The maximum score for each group in a particular time interval is 15.**

Three of these donkeys were from Group DB and the other donkey was from Group D. The irregular respiratory pattern appeared in the Group D donkey only after butorphanol was administered to correct insufficient sedation and analgesia. The respiratory rates for the donkeys are graphically displayed in Fig. 6.

Adverse reactions

Two donkeys from Group D showed pain in response to surgical manipulation. Another 2 from Group D were agitated during the procedure. These problems developed within 10 min of administration of detomidine. One donkey went down in the crush after receiving 20 μg/kg detomidine and 50 μg/kg butorphanol. This was an unintentional error due to miscalculation of drug dosages. The results relating to this donkey were not included in the analysis. The donkey was treated with yohimbine (Yohimbine, Centaur Laboratories) (0.25 mg/kg), and replaced with another donkey in the trial. Two donkeys urinated during or shortly after the procedure. Both these donkeys were from Group DB. One donkey from Group DB developed obvious facial muscle twitches. The complications are recorded in Table 3.

DISCUSSION

The recommended dose of detomidine in donkeys is 20 μg/kg and this provides both analgesia and sedation[19]. Lower doses did not produce analgesia[19]. Detomidine has been used in doses ranging from 10–20 μg/kg for clinical sedation and this dose range has been found highly effective in horses[3,4,6,21]. Higher doses of detomidine have been recommended to increase analgesia and prolong sedation in horses[4,11]. It has been suggested that donkeys require a higher dose of detomidine for sedation than horses[9,19,29].

Butorphanol is 7, 20 and 40 times more potent than morphine, pentazocine and pethidine respectively as an analgesic in laboratory animals[20,22]. At a dose of 400 μg/kg, butorphanol is capable of relieving superficial pain for 30 min and visceral pain for 90 min in horses[14,20]. Butorphanol is less effective in increasing visceral pain threshold than xylazine but more effective than morphine, levorphanol and flunixin[14]. A dose of less than 50 μg/kg resulted in poor superficial analgesia but effective visceral analgesia[13]. The analgesic effect, duration and depth are dose-related[13]. Doses of more than 220 μg/kg intravenously are associated with excitation, ataxia and muscle twitches, while doses of 100 μg/kg produce minimal side-effects[20,22,23]. High doses of butorphanol will result in an antago-

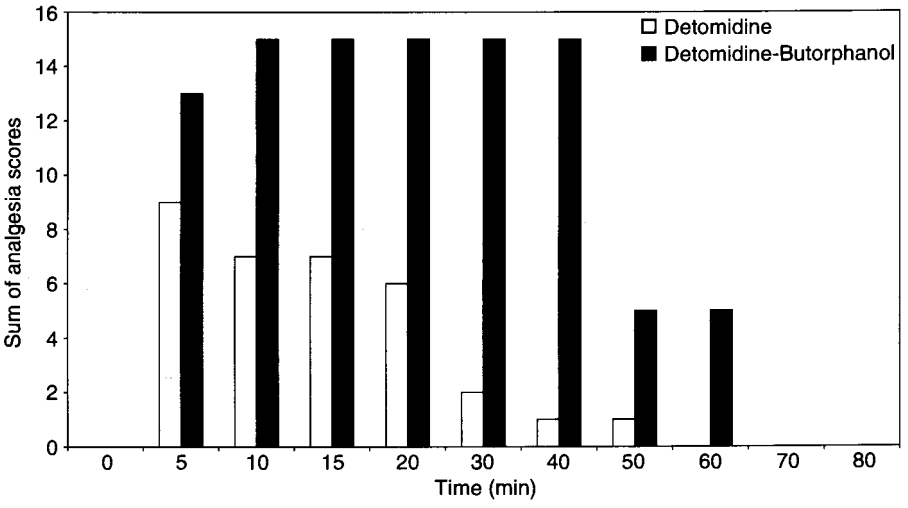

Fig. 2: **Analgesia scores for the pain tests conducted around the ears. The scores for each time interval for each group were summed. The maximum score for each group in a particular time interval is 15.**

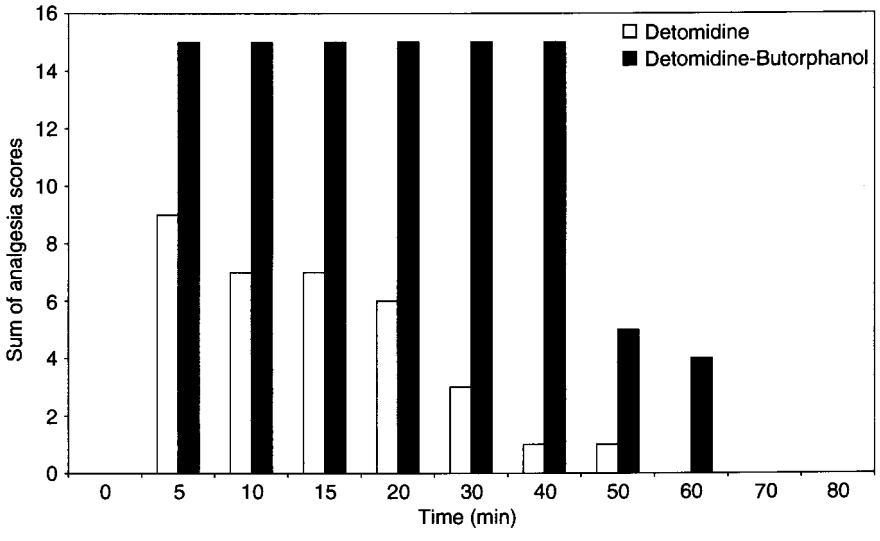

Fig. 3: **Analgesia scores for the pain tests conducted on the shoulder. The scores for each time interval for each group were summed. The maximum score for each group in a particular time interval is 15.**

Table 3: **Adverse reactions.**

Adverse reaction[a]	D[b]	DB[b]	Total	Remarks
Sedation inadequate	3*	0	3	
Add butorphanol	2	0	2	
Add detomidine	1	0	1	
Kicking	1	0	1	
AV block	1*	0	1	*After an additional dose of detomidine
SA block	0	1	1	
Erratic respiration	1*	3	4	*After an additional dose of butorphanol
Painful	2	0	2	
Agitated	2	0	2	
Full bladder	0	2	2	
Facial ticks	0	1	1	
Went down	0	1*	1	*Given 20 μg/kg detomidine and 50 μg/kg butorphanol inadvertently

[a]The complications are recorded in terms of the number of donkeys developing each type of complication.
[b]D = detomidine group; DB = detomidine-butorphanol group.

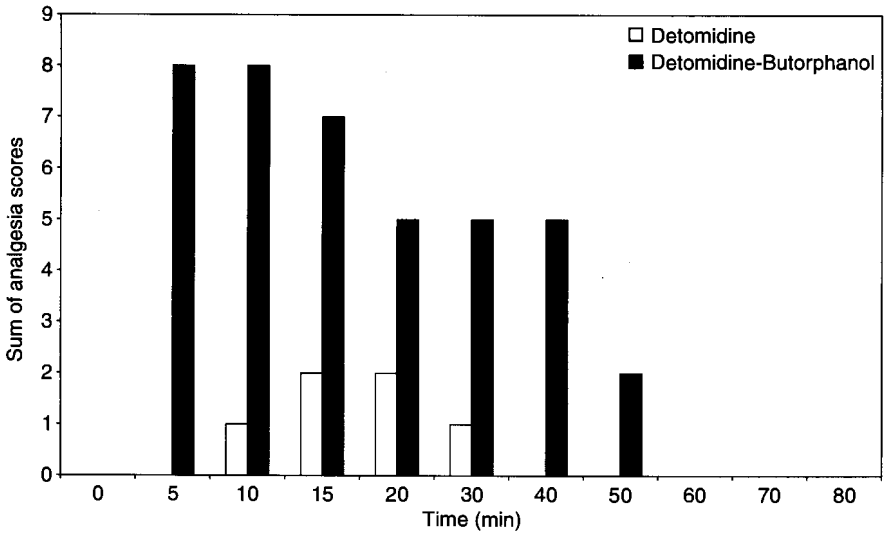

Fig. 4: **Analgesia scores for the pain tests conducted on the coronary band. The scores for each time interval for each group were summed. The maximum score for each group in a particular time interval is 15.**

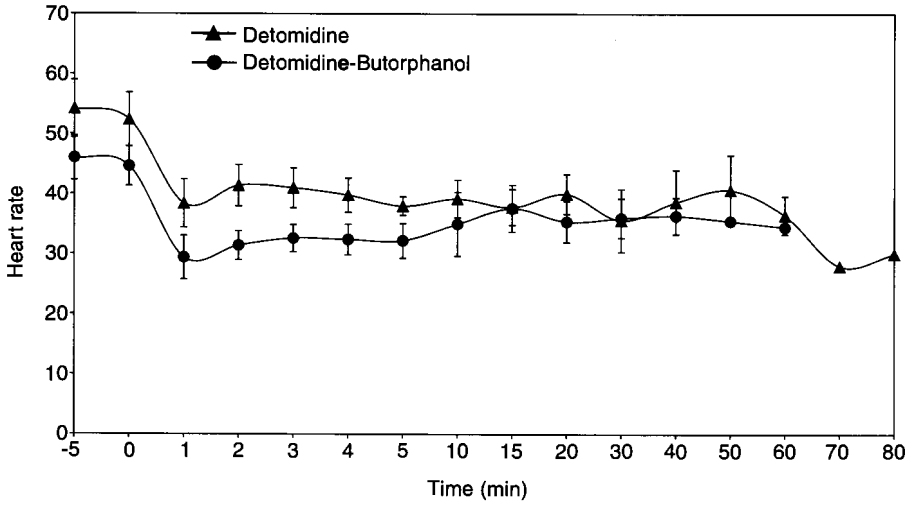

Fig. 5: **Mean heart rate for both groups in beats per minute as a function of time. Error bars indicate the standard error of the mean.**

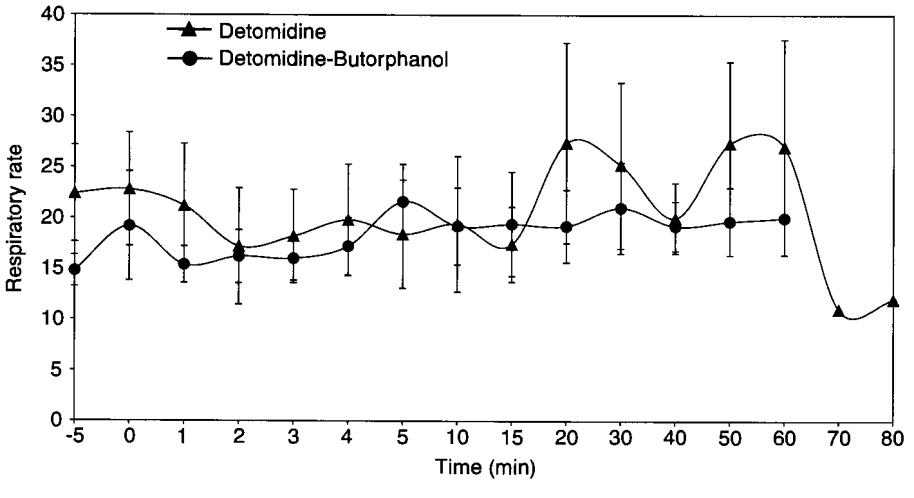

Fig. 6: **Mean respiratory rates for both groups in breaths per minute as a function of time. Error bars indicate the standard error of the mean.**

nising effect with reversal of analgesia[19]. Cardiopulmonary effects are minimal when administered in analgesic doses although butorphanol may induce tachycardia[15,21,24]. These minimal cardiovascular effects are reflected in studies performed in humans and dogs[24]. Butorphanol is a potential respiratory depressant but the observed changes in partial pressure of oxygen and carbon dioxide are not statistically significant[15,23,24,27]. The cardiovascular and respiratory abnormalities are more prominent in pain-free animals[23].

A dose of 10 μg/kg of detomidine in combination with 25–50 μg/kg of butorphanol has been used[3,17,27] to achieve neuroleptanalgesia. The detomidine can be given 5 min before administration of butorphanol[3], or the butorphanol can follow immediately after the detomidine[27]. Sedation is easily extended by additional doses of either detomidine or butorphanol or both[27]. Excitation shortly after the administration of this combination has been noted[3]. Sedation is more profound than if detomidine alone is used, and horses are apparently unaffected by sounds, tactile stimuli and surrounding activity[27]. Blood pressure effects are minimal after administration of detomidine and butorphanol[3]. The combination did not significantly alter the arterial partial pressure of carbon dioxide and oxygen[3,17]. Ataxia is not severe and depends on the dose of detomidine given[3,27]. It constitutes a potential danger, but most horses appear to 'wake up' and correct their balance before becoming sedated again[27]. Heart rates drop dramatically after administration of the combination of both drugs[27], probably owing to the detomidine component.

Drug dosages

Previous workers have shown that a dose of 10 μg/kg detomidine produced poor analgesia and mild sedation in donkeys[20]. The donkeys sedated with detomidine alone exhibited a deep pain response at the coronary band. Detomidine cannot be used for moderately to severely painful procedures in donkeys without additional analgesia. It is concluded that detomidine is not as effective an analgesic in the donkey as it is in the horse. The average dose of butorphanol was 28 μg/kg. These doses of detomidine and butorphanol correlate well with dosages recommended for use in equines[3,17,27].

Sedation and analgesia

The 2 donkeys used in the pilot trial were cast with the aid of ropes and neutered on the lawn. These 2 donkeys received 20 μg/kg detomidine and 50 μg/kg butorphanol. This procedure

was carried out in order to assess the effect of a higher dose of these drugs. One donkey received detomidine only while the other donkey received both drugs. Neither of these donkeys showed severe ataxia, nor were they easily cast. It was soon evident that the combination of detomidine and butorphanol produced a greater sedative and analgesic effect than detomidine alone. It was surprising that 1 donkey went down in the stocks. Subsequently 7 more donkeys have been castrated using the combination of detomidine and butorphanol at higher doses, and none showed a tendency for recumbence. The donkey went down approximately 4 min after the administration of detomidine (20 μg/kg) and butorphanol (50 μg/kg) in the stocks. This period coincides with the maximum sedative effects of these drugs. The donkey was also being positioned in the crush at the time and it is possible that it slipped and was unable to stand up in the narrow stocks. It was in poor bodily condition, which may have played a role. The remainder of the procedure was performed without additional sedation after the detomidine was partially reversed with yohimbine. No other donkeys went down and the sedation and analgesia proved sufficient at the reduced doses. Detomidine and butorphanol should be used with caution in patients in poor condition.

The donkeys sedated with detomidine only continued to exhibit a deep pain response on the coronary band. They were sedated for approximately 20 min only. A dose of 10 μg/kg of detomidine alone is thus insufficient for standing procedures in the donkey. Other researchers have shown that this dose produced poor analgesia with mild sedation in donkeys[20]. However, a dose of 10 μg/kg has been shown to be an effective sedative and analgesic in horses[4,5].

The failure of detomidine to produce sufficient sedation on its own in the equine has been reported[3–5,7,8,26]. One donkey in the trial had the ability to kick accurately when stimulated with painful stimuli under detomidine sedation alone. The reaction of a single donkey is of limited value but this should be borne in mind when using this drug on its own. Early in this trial it became evident that the combination of detomidine and butorphanol produced better analgesia and sedation than detomidine alone. The pain and analgesia scores support this hypothesis. For this reason, later in the trial butorphanol was given when the detomidine alone failed. Detomidine and butorphanol used at a dose of 10 μg/kg and 25 μg/kg, respectively, constitute an effective combination for standing procedures, allowing 60 min of sedation and providing analgesia. The superior sedation is the result of synergistic effects between detomidine and butorphanol.

The average length of sedation with detomidine alone was 20 ± 10 min. This is of shorter duration than reported for donkeys (35 ± 4.01 min)[20]. The average length of sedation provided by the combination of detomidine and butorphanol was 67 ± 19 min. This correlates with what has been reported for equines[4,5].

Cardiovascular changes

After intravenous injection of alpha$_2$ adrenergic agonists, the following cardiovascular effects have been described. Blood pressure initially increases rapidly due to direct stimulation of peripheral alpha$_1$ receptors[3–5,26], which increases systemic vascular resistance, usually within 2–5 minutes of administration[3–5,25,26]. This is accompanied by a significant fall in heart rate due to a baroreceptor response[3–5,25,26]. The duration of bradycardia is unpredictable[4,20]. After the hypertension, there is a centrally mediated drop in systemic vascular resistance and sympathetic tone, and more prolonged mild hypotension ensues[3–5,25]. The heart rate usually returns to normal with in a few minutes[5,26]. The cardiovascular side-effects are dose-dependent and reach their maximum effect 15–30 min after intravenous injection[5]. Central venous pressure and pulmonary capillary wedge pressure are not altered by detomidine in horses[25]. Cardiac output and tissue perfusion are reduced, although no clinical problems due to low tissue perfusion have been reported[4,5,20,25].

Heart rates decreased significantly over the first minute. This correlates well with what has been reported in equines treated with detomidine with or without butorphanol, and with the single account of the use of detomidine in donkeys[4,5,7,8,20,26]. This should coincide with the maximum increase in blood pressure associated with the direct stimulation of peripheral alpha$_1$ receptors[3–5,26]. After the initial drop, the heart rate tended to return to baseline values. It is well-known that after administration of alpha$_2$ adrenergic agonists the heart rate tends to return to normal, usually within 20–30 min. The donkeys were not acclimatised to the crush, as this would have defeated the object of assessing the combination of drugs under field conditions. The stress of the new environment and handling of the animals during preparation may have increased the baseline heart rates owing to an increase in sympathetic tone. The observations of both an atrioventricular and a sino-atrial block have been reported in the equine following the administration of these drugs[3–5]. Both these arrhythmias are well described after the use of alpha$_2$ adrenergic agonists and result from a decrease in sympathetic tone and an increase in parasympathetic tone.

Respiratory changes

The Cheyne-Stokes respiratory pattern was recognised with the aid of a capnography. The capnograph has been used to evaluate respiratory patterns with the sampling line in the ventral meatus of small animals[19]. The Cheyne-Stoke respiratory pattern is the result of altered functioning of the respiratory centres in the brain[11]. Hypoventilation results in a rise in the arterial partial pressure of carbon dioxide. The chemoreceptors detect the increased partial pressure of carbon dioxide in the arterial blood, and relay the information to the central nervous system to increase ventilation. Hyperventilation over-compensates for raised carbon dioxide levels, and the arterial partial pressure of carbon dioxide drops below normal. The chemoreceptors stop responding and apnoea follows[11]. Possible mechanisms include altered blood flow, damage to peripheral chemoreceptors and central nervous system damage. Opioids have been reported to cause Cheyne-Stokes respiratory pattern[6].

Opioids and alpha$_2$ adrenergic agonists are known to depress ventilation and alter arterial partial pressures of carbon dioxide and oxygen. None of the donkeys showed any symptoms of intra- or post-operative hypoxia or respiratory failure. The possibility of hypoxia has been noted in equines but has never been found to be clinically significant. Blood-gas analysis was not performed. We could find no report of a Cheyne-Stokes respiratory pattern in horses in relation to detomidine and/or butorphanol. The technique of insertion of the capnograph into the ventral meatus has not been evaluated as an experimental tool, but the use of tubing placed into the trachea has been evaluated[19]. The difference in respiratory gas composition between the ventral meatus of a nostril and the upper part of the trachea should be negligible. The nasal passageways humidify the air and it is possible that the inspired gases would not be completely humidified when analysed by the capnograph on inspiration. When the individual readings of respiratory rate are analysed for each donkey, the respiratory rate was very erratic between readings. In view of this, it is difficult to find a statistical difference in the respiratory rates, which explains

the irregular nature of the respiratory graph.

Relaxation of the laryngeal and nasal alar muscles owing to detomidine predisposes horses to upper airway obstruction and stridor[5]. This reduction in airway diameter has not been associated with any clinical symptoms but it may cause arterial hypoxaemia[5].

Adverse reactions

The diuresis induced by detomidine is associated with increased glomerular filtration rates, inhibition of anti-diuretic hormone release, inhibition of anti-diuretic hormone effect on the renal tubules and increased release of atrial natriuretic factor[5,7]. Two of the donkeys did void their bladders during or shortly after the procedure. This should be borne in mind, especially when urogenital operations are planned. The mechanisms responsible for this are similar to those described for alpha$_2$ adrenergic agonists.

CONCLUSION

Detomidine alone, at a dose of 10 μg/kg, should not be used without additional analgesia for moderate or severely painful procedures in donkeys. A dose of 10 μg/kg of detomidine with 25 μg/kg of butorphanol was found effective for standing procedures with minimal clinical side-effects. Sedation and analgesia are expected to last approximately 60 minutes.

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Chapter 4

Material and Methods

Pilot Trial

Donkeys 2 and 4 were cast with the aid of ropes and then castrated on the lawn. These two donkeys received 20 µg/kg of detomidine and 50 µg/kg of butorphanol. This was done in order to assess the effect of a higher dose of these drugs. One donkey received detomidine only while the other donkey received both drugs. Neither of these donkeys showed severe ataxia nor were they easily cast. It was evident early on that the combination of detomidine and butorphanol produced a greater sedative and analgesic effect than detomidine alone.

Materials and Methods

Twelve healthy male donkeys, between the ages of 6 months and 15 years were used in the trial. These donkeys were part of a trial to evaluate a novel surgical technique for the castration of donkeys laprascopically. The donkeys were randomly assigned to one of two groups by drawing lots. One group received detomidine only (D) while the other group received detomidine and butorphanol (DB). Each animal was identified by means of a freeze branded number on the withers. The allocation of the animals is shown in Table 4. The surgeons performing the procedure and selected observers were blind as to what drug had been given. All the donkeys were sedated to facilitate their surgical procedure. Donkeys 2 and 4 were used as part of pilot trial and were castrated by means of a standard castration procedure[59] as described for equines. These donkeys' results were not included for analysis. The remaining ten donkeys had the testicular artery ligated laprascopically with a Filshie clip as described by Briggs et al[4].

Table 4: Donkey Allocation

Random allocation of treatment protocols

Group No	Donkey Number
D	4
Detomidine	9
	11
	22
	3
	14
DB	2
Detomidine	20
Butorphanol	1
	8
	25
	31

Before the commencement of the trial, a complete physical examination and blood count was done in order to establish clinical normality. Preoperative serum samples were taken and stored to be analysed if required. All animals were weighed on a suitable scale and their body mass recorded. Clinical findings and abnormalities were recorded on the form described in Annexe 1.

The donkeys were starved for 24 hours before the trial and ad lib water was allowed until the time of the trial. The animals were housed outside in paddocks. The preparation involved the following: an area over the left jugular grooves, the left shoulders, sternum and pectoral muscles were shaved. The jugular groove was surgically prepared. A 1 ml bleb of local anaesthetic[a] was placed subcutaneously over the jugular vein and an intravenous Teflon catheter[b] was placed into the left jugular vein. The intravenous catheter was then sutured into place. This catheter was used for all intravenous drug administrations. The catheter was flushed regularly with heparinised saline to ensure that it remained patent throughout the trial. The donkeys were then lead inside and restrained in stocks. Electrocardiograph (ECG) electrodes were placed in a base apex configuration on shaved areas of the left shoulder, sternum and pectoral muscles. The ECG electrodes were connected to an ECG monitor[c]. The collecting tube from a capnograph[d] was introduced 8 – 10 cm into the left ventral nasal meatus.

All data was recorded at the following time intervals: –5, 0, 1, 2, 3, 4, 5, 10, 15, 20 minutes and then every ten minutes thereafter until the procedure was finished. Heart rate and rhythm was monitored using an ECG machine. Rhythm abnormalities were recorded in terms of frequency, type and length of time after the administration of the drugs. Respiratory rate and rhythm were monitored physically through chest wall movement and on the capnograph to detect apnoeic periods. Respiratory rate was recorded at the time intervals stipulated above. Respiratory rhythm abnormalities were recorded. Mucous membrane colour and capillary refill times were monitored and abnormal findings were recorded.

Donkeys in Group D received 10 μg/kg of detomidine[e] and donkeys in Group DB received 10 μg/kg of detomidine and 25 μg/kg of butorphanol[f] at time 0. Additional doses of detomidine and/or butorphanol at a quarter to a half of the original dose were given when the degree of sedation or analgesia was considered insufficient. The sedation or analgesia was considered insufficient when the donkeys moved in response to surgical stimuli, were restless in the stocks or the sedation or analgesic score was one or less. These additional doses were recorded in Table 10. Donkeys that received additional doses of either butorphanol or detomidine were given a score of zero for sedation and analgesia for evaluation purposes from that point onwards.

Table 5: Sedation Scoring Table

Score	Behaviour
0	No Sedation
1	Mild Sedation
2	Moderate Sedation
3	Heavy Sedation

Sedation was characterised by lowering of the head, relaxation of the upper eyelids, drooping of the lower lip and dropping of the ears. The sedation was graded according to a numerical scale; 0 – No sedation, 1 – Head normal position, relaxed lower lip and eyelids, 2 – Head lowered, drooping eyelids and lip, 3 – Head fully lowered, drooping eyelids and lips (Table 5)[58]. The time to onset of sedation was recorded.

[a] Lignocaine 2%, Centaur Laboratories (Pty) Ltd
[b] Intraflon, AME Medical (Pty) Ltd
[c] Cardiocap II, Datex,
[d] Ultima Capnomac, Datex
[e] Domosedan, Novartis Animal Health
[f] Torbugesic, Forte Dodge Animal Health

The degree of analgesia was assessed by the response of the animal to a needle pinprick applied to the base of the ear, shoulder and front hoof's coronary band[32 47]. The analgesia was scored according to a numerical rating scale; 0 – No analgesia, 1 - Conscious awareness and subdued response, 2 - Awareness but no response, 3 - No response to test (Table 6)[10 16 58]. The use of numerical rating scales for the assessment of pain is a useful tool but the sensitivity of this scale in detecting small differences is limited[5]. Responses to analgesia tests were recorded at time 0 and thereafter at 5, 10, 15, 20 minutes and every 10 minutes thereafter.

Table 6: Analgesia Scoring Table

Score	Response
0	No analgesia
1	Conscious awareness, Reflex response.
2	Awareness of pinprick
3	No response to test

The time to the end of sedation was recorded. The surgeon performing the procedure and the observers assessed the degree of analgesia and sedation on a subjective basis using the response to surgical stimuli and the ability to complete the procedure with minimum discomfort to the donkey. When additional doses of detomidine and/or butorphanol were required, this was used as the end time of sedation. All data collected was recorded on the monitoring form described in Annexe 2.

Animals developing clinical abnormalities were treated appropriately according to accepted practices. All abnormal clinical findings and treatments were recorded.

Statistical Analysis

Comparison between groups of weight, age, drug dose and procedure time was done using the student's t test. For sedative and analgesic times, an ANOVA analysis for two way variance and the Mann-Whitney Rank Sum test were used. The statistical difference set at 0.05. All data from each Group was analysed for means, standard deviations and modes. Heart and respiratory rates were analysed within each group and between groups. The data from times –5 and 0 minutes were pooled when data was analysed with reference time 0. Graphs were used to show trends (blood pressure, respiratory rate). Sedative and analgesic scores were summed separately for each time interval. The summed values were used for analysis and these were graphed. Histograms were also used to determine the distributions of a particular sedative or analgesic score in each of the two groups. Due to incomplete data for the 70^{th} and 80^{th} minute time interval certain analysis were only performed to the 60^{th} minute time interval. Statically analysis was performed with SigmaStat for Windows, Version 2.00, Jandel Corporation and SigmaPlot for Windows, Version 4.00, SPSS Incorporated. Spreadsheets were created with Microsoft's Excel 97 SR-1, Microsoft Corporation.

This trial was approved by the Research and Ethics committees of the Faculty of Veterinary Science at the University of Pretoria (Project Number: 36.5.97).

Chapter 5

Results

Clinical Examination

The donkeys ranged in age from 6 months to 13 years. Group D had an average age of 2.4 years and that of Group DB was 7.4 years. Despite this great discrepancy in average age, very little statistical difference exists between the two groups, (P >0.05), Table 21. The discrepancy in the average age is the result of a single donkey in group 2 having an age of 13 years and the small number of donkeys in each group makes this statistical difference inevitable. The ages are summarised in Table 7. The body mass of the animals varied from 90.00 kg to 180 kg. The average mass of Group D was 144.00 kg and that of Group DB was 138.80 kg. No statistical difference was found between the body masses of the two groups, (P > 0.05), Table 22. The body masses are summarised in Table 7. Donkey 9 was in a poor condition.

Table 7: Age and Body masses of Donkeys

Group D	Detomidine					
Donkey No:	1	8	25	31	20	Mean
Age (years)	0.5	4	3	1.5	3	2.4
Body mass (Kg)	168.00	146.00	122.00	120.00	164.00	144.00

Group DB	Detomidine-Butorphanol					
Donkey No:	22	11	3	14	9	Mean
Age (years)	13	1.5	6	15	1.5	7.4
Body mass (Kg)	126.00	90.00	180.00	162.00	136.00	138.80

The haematology profiles are recorded in Table 14 and were compared to the normal values[19] [63] in Table 13. Three of the donkeys were diagnosed on blood smear with *Babesia equi* and were treated with imidocarb[9] [20]. Four donkeys had haematocrits of less than 30 %. Three donkeys had thrombocyte counts of less than 200 $x10^9$/l. Five donkeys had white cell counts of greater than 10 $x10^9$/l with corresponding abnormalities in their respective white cell series. Monoblast activity was high in three donkeys. The donkeys infected with babesia did not have any physical signs of disease at the time of examination. No other clinical abnormalities were evident.

Donkeys 2 and 4 were used as pilot trial to ensure that the drug doses were sufficient. These donkeys were given 20 µg/kg of detomidine and 50 µg/kg of butorphanol. No complications were recorded and these animals were excluded from the results.

Drug Doses

The doses of drugs given to the ten donkeys included in the trial are recorded in Table 11 and Table 12. The average dose for detomidine was 11.24 µg/kg and that of butorphanol was 28.0 µg/kg. Initially Group D received 9.861 µg/kg of detomidine while Group DB received 10.088 µg/kg of detomidine and 29.539 µg/kg of butorphanol. There was no statistical difference between the two groups with respect to the initial dose of detomidine given (P = >0.05) (Table

[9] Forray 65, Hoechst Ag-Vet

23). The average dose of detomidine given to Group D after additional doses of detomidine was 10.556 µg/kg. The average additional dose of butorphanol given to Group D was 24.306 µg/kg. Group DB did not receive any additional doses of detomidine or butorphanol for analgesia or sedation.

Sedation and Analgesia

Sedation

The time to onset of sedation (sedative score >=2) was 4 minutes 21 seconds in Group D compared to 3 minutes 28 seconds in Group DB (Table 8). The onset of sedation was more rapid in Group DB than in Group D and this was statistically significant, ($P < 0.05$) (Table 24). The average length of sedation for Group D was 20 minutes and that of Group DB was 1 hour 7 minutes and 46 seconds (Table 8). This was statistically significant, ($P < 0.05$) (Table 25). A sedative score of 3 was only maintained for 10 minutes in Group D compared to 40 minutes in Group DB. Two donkeys in Group D did not achieve a score of 3 while all donkeys in Group DB did. All donkeys in Group D had achieved a score of 1 by 20 minutes while most of the donkeys in Group DB had a score of 3 at the same time interval. Sedation scores obtained for Group D at time intervals 5, 10 and 15 were not statistically different from each other, however there was statistical difference between time interval 5 and time interval 20 and 30 ($P< 0.05$). There was no statistical difference for Group DB between time intervals 5, 10, 15, 20, 30 and 40 but there was statistical difference between tine interval 5 and time interval 50 and 60 ($P< 0.05$). By the end of the procedure, most donkeys in Group DB had a score of 2 while the Group D donkeys had no score. Donkeys receiving butorphanol, when sedation was no longer adequate, readily obtained a score of 3. In summary, sedation was of a shorter duration and lower intensity in Group D than in Group DB (Table 17 a, b, c, Figure 1). Sedative scores were graphed according to the sum of sedative scores for each time interval. The difference in sedative scores became more apparent when additive sedative score graphs (Figure 2) and the histogram (Figure 3) is viewed.

Analgesia

Around the head, Group D produced mode score of 2 at 5 minutes, which lasted for 20 minutes. Group DB produced a mode score of 2 at 5 minutes and 3 at 10 minutes. In Group DB, the score was maintained for at least 40 minutes. Similar results are seen for the analgesia tests conduct on the shoulder area. There was no statically difference between time interval 5 and any of the other time intervals for Group D for analgesia around the head and shoulder until time interval 30. This was statistically significant ($P< 0.05$). In Group DB there was no statistical difference between time interval 5 and any of the time intervals up to interval 50 for analgesia around the head and shoulders. Interval 50 was statistically different from interval 5 ($P< 0.05$). In Group D, coronary band was not attenuated at any point in time while in Group DB a score of 2 was achieved. In Group D there was no statistically significant difference between time interval 5 and any of the other time intervals for coronary band analgesia. In Group DB no statistical difference existed between time interval 5 any of the other time intervals until interval 50 ($P< 0.05$). In general, the analgesia lasted twice as long and was of a greater intensity in Group DB compared to Group D. The analgesic scores for the various pain tests are laid out in Tables 18 – 20 and Figures 5 - 13. The difference between detomidine alone and detomidine-butorphanol is also more apparent when the additive analgesic scores are graphed (Figure 11, Figure 12 and Figure 13) and the histograms are viewed (Figure 8, Figure 9 and Figure 10). The three donkeys requiring additional sedation and analgesia were from Group D. Donkeys 1 and 31 received additional doses of butorphanol while Donkey 8 received an additional dose of detomidine.

Procedure Times

The median times of the procedures performed in Group D and Group DB were of a similar length, 45 minutes 31 seconds and 43 minutes respectively, and was not statistically different, (P >0.05), Table 8 and Table 26.

Table 8: Times recorded during the procedure

Group 1	Detomidine					
Donkey No:	1	8	25	31	20	Average
Onset Of sedation	0:04:16	0:04:28	0:04:50	0:04:08	0:04:03	0:04:21
Length of Sedation	0:14:20	0:21:32	0:21:12	0:08:52	0:36:08	0:20:25
Length of Procedure	0:57:31	1:22:00	0:18:06	0:21:19	0:48:40	0:45:31

Group 2	Detomidine-Butorphanol					
Donkey No:	22	11	3	14	9	Average
Onset Of sedation	00:03:38	0:03:28	0:03:28	0:02:56	0:03:49	00:03:28
Length of Sedation	1:29:16	1:27:13	0:59:15	0:43:54	0:59:11	1:07:46
Length of Procedure	00:42:00	0:30:12	0:54:32	0:39:45	0:48:30	00:43:00

Cardiovascular and Respiratory Changes

Pre-treatment heart rates were 53.3 and 45.3 beats per minute for Group D and Group DB respectively. This dropped to 38.4 and 29.4 in the first minute after treatment for Group D and Group DB respectively. The drops in heart rates are statistically significantly and remained significantly decreased through the entire procedure (P <0.05) (Table 27). There was however no statistical difference between the two groups at any point in time, Table 28. The heart rates are recorded in Table 15 and are graphically represented in Figure 14. One donkey in Group D developed an atrioventricular block while another donkey in Group DB developed a sinoatrial block.

The respiratory rates tended to decrease in the first few minutes after which the rate stabilised. There was however no statistically significance in the drop in respiratory rate (Table 29). Four donkeys had irregular respiratory patterns. Three of these donkeys were from Group DB and the other donkey was from Group D. The irregular respiratory pattern only appeared in the Group D donkey after butorphanol was administered due to insufficient sedation and analgesia. There was no statistical difference between the two groups concerning respiratory rate (Table 30). The respiratory rates for the donkeys are recorded in Table 16 and graphically displayed in Figure 15.

Adverse Reactions

Two donkeys from Group D showed pain in response to surgical manipulation. Another two from Group D were agitated during the procedure. These problems developed within 10 minutes of the administration of detomidine. One donkey went down in the crush after receiving 20 µg/kg of detomidine and 50 µg/kg of butorphanol. This was an unintentional error due to a miscalculation of drug doses. The results of this donkey were not analysed. This donkey was treated with yohimbine[h] (0.25 mg/kg). Another donkey replaced this donkey in the trail. Two donkeys urinated during or shortly after the procedure. Both these donkeys were from Group DB. One donkey from Group DB developed obvious facial muscle twitches. The

[h] Yohimbine, Centaur Laboratories (Pty) Ltd

complications are recorded in Table 9: Complications. Donkey 3 died 6 days after the trial due to babesiosis.

Table 9: Complications observed after detomidine and detomidine-butorphanol administration in donkeys.

Complication	D	DB	Total	Donkey No	Notes
Sedation inadequate	3		3	1,8,20,31	All from the Detomidine group
Add Butorphanol	2		2	1,31	Butorphanol more effective
Add Detomidine	1		1	8	
Kicking	1		1	8	
AV Block	1		1	8[1]	[1] After additional dose
SA Block		1	1	14	
Erratic Respiration	1	3	4	31[2],11,3,14	[2] After additional butorphanol
Painful	2		2	8,31	
Agitated	2		2	1,8	
Full Bladder		2	2	11,3	
Facial Twitches		1	1	14	
Went Down		1	1	9	Given 20µg/kg Detomidine And 50µg/kg Butorphanol

D = Detomidine Group, DB = Detomidine-butorphanol Group

Chapter 6

Discussion

Materials and Methods

Sedation

The evaluation of pain and sedation is very often dependent on subjective criteria[23]. Although potential flawed very few objective tests are available for these two aspects[23]. Variation in individual interpretation of subjective parameters can be enormous but the variation can be reduced by using the same observers each time[24]. A good understanding of normal behaviour is an important prerequisite[23].

Sedation has been evaluated using changes in the position of head, relaxation of the lower lips and the dorsal eyelid[47]. The degree of change is then correlated to a descriptive score of none, mild, moderate or profound sedation[47]. A numerical score attached to a number of descriptive terms has been used[27 46]. Clinical signs of sedation have been used as an evaluation tool[44]. These signs include lethargy, little or no response to visual or vocal stimulation, immobility and ataxia[16 44]. Sedation and analgesia have been evaluated subjectively in terms of the ability to complete a procedure with the minimum amount of discomfort to the animal[11].

Sedation has been incorrectly correlated with a loss proprioception and pain[6 58]. In this study the response to stimulation of the coronary band and ear were used. Sedation is a state of central nervous system depression associated with a loss of anxiety but not necessarily analgesia. Some sedatives do produce analgesia as well; alpha$_2$ adrenergic agonists are an example of such a drug.

An objective assessment of sedation has been obtained by measuring the distance of the chin from the floor[16].

In this study, due the restraint in stocks and the continual movement of people around the animal during the procedure the measurement of the chin-floor distance was not feasible. Instead, sedation was evaluated using the relaxation of lower lip, upper eyelid and the lowering of head were used[43 58]. Additional clinical signs such as lethargy, response to environmental stimuli (noise, movement of people) and response to surgical manipulation were used. This was then correlated to a numerical score with descriptive terms.

Analgesia

A technique for the evaluation of pain was devised in 1972 using a pinprick response on predetermined areas of the fore- and hindlimbs, trunk and neck[32]. The pinpricks are applied to the forelegs (coronary band and carpus), hindlimb (coronary band and tarsus), trunk (neck, shoulder and hindquarter) and the head (base of ears)[32]. The response to the pinprick is then correlated to a descriptive[47] or numerical score[10 16 58]. The descriptive score includes no response, weak or normal[47]. A descriptive or numerical score can be correlated to a number of descriptive terms to assess the severity of pain[27 28]. Clinical signs of pain and discomfort are also used to evaluate pain and again here either a descriptive or a numerical rating

system is used[44]. Clinical signs used include sweating, kicking, pawing and head movements[44 27].

Superficial pain has been objectively evaluated using a heating lamp focused on a blackened area of skin (coronary band), an accelerometer attached to the limb and a timer was then used to determine the response time. The delay in response is used to assess the degree of analgesia[31]. Visceral pain has been objectively evaluated with a caecal balloon model[31]. In this model, the pressure in the balloon and the delay time in response to the inflation of the balloon are used as objective parameters[31]. Somatic analgesia has been evaluated using the application of towel clamps and a skin incision[51].

Touching of the cannon and coronary band with needle and the stimulation of the inside of the ear have been found to the most effective stimuli for evaluation[10]. More recently, pain has been evaluated in small animals using a scoring system based on physiological and subjective parameters[24]. This has not yet been evaluated in equines. The use of numerical rating scales for the assessment of pain is a useful tool but the sensitivity of this scale in detecting small differences is limited[5].

The hindquarters and flank were draped as part of the surgical preparations of the donkey and therefore were not available for the assessment of pain. The use of pinpricks is well described to evaluate the analgesic effects of alpha$_2$ adrenergic agonists. This method is easy to perform, required no equipment and has been evaluated in donkeys previously[43]. This method was adjusted to a numerical score and used.

Selection of Drug Dose

The only description of detomidine in donkeys recommended a dose of 20 µg/kg as the dose that provides both analgesia and sedation[43]. Lower doses did not produce analgesia[43]. Detomidine has been used in doses ranging from 10 – 20 µg/kg for clinical sedation and this dose range has been found highly effective[11 12 16 47]. Higher doses of detomidine have been recommended to increase analgesia and prolong sedation[12 27]. It has been suggested that donkeys require a higher dose of detomidine for sedation than horses[29 43].

The dose of butorphanol in horses has been recommended at 200 – 400 µg/kg when used on its own[31 44]. Butorphanol and detomidine is an effective combination especially when detomidine has failed[10 11 17]. This combination is undoubtedly synergistic[58]. A dose of 10 µg/kg of detomidine in combination with 25 to 50 µg/kg of butorphanol has been used in horses[10 36 58]. One donkey went down in the crush after receiving 20 µg/kg of detomidine and 50 µg/kg of butorphanol.

In view of the above, it was decided to use detomidine at 10 µg/kg and butorphanol at 25 µg/kg. This low dose of detomidine has been shown not to have analgesic properties. Part of the aim of this trial was to show that the combination of detomidine and butorphanol produces superior sedation and analgesia. If the detomidine dose was increased in the detomidine only group, this comparison might not have been possible. In order to ensure patient comfort a rescue plan was included to alleviate any suffering.

Clinical Examination

The information regarding the occurrence and importance of babesiosis in donkeys is limited. Three donkeys in this trial were found infected with babesiosis on examination of blood smears. Of these donkeys, one donkey was severely anaemic while another one was moderately anaemic. None of these donkeys showed overt clinical signs of babesiosis. One donkey died shortly after completion of the trial due to babesiosis. No parasites were found on

this donkeys blood smear before the trial nor were clinical signs evident. Horses can have very low parasitaemias and the diagnosis of babesiosis is easily missed on a blood smear[13]. Acute death in horses and donkeys due to babesiosis has been described[2 13 26]. It is also known that a subclinical "carrier" state of babesiosis occurs in horses and donkeys and can flare up during times of stress[2 13 26]. It is plausible that the stress of the procedure in the donkey resulted in immunosuppression and a flaring up of subclinical babesiosis. Corticosteroid induced immunosuppression has been shown to increase the incidence and severity of babesiosis in donkeys[48]. Comparison of the blood results of the donkeys did not reveal any useful information with respect to the status of babesiosis in these animals.

Drug Doses

The average dose of detomidine used in this trial was 11.24 μg/kg. Previous workers have shown that this dose produced poor analgesia with mild sedation in donkeys[43]. However a dose of 10.00 μg/kg has been shown to be an effective sedative and analgesic in horses[11,12]. The donkeys sedated with only detomidine still exhibited a deep pain response at the coronary band. Detomidine alone cannot be used for moderate to severely painful procedures in donkeys without additional analgesia. It is concluded that detomidine is not as an effective analgesic in the donkey as it is in the horse. The average dose of butorphanol was 0.028 mg/kg. These doses of detomidine and butorphanol correlates well with what has been reported in the literature for use in equines[10 36 58].

Sedation and Analgesia

Donkey 9 went down in the stocks approximately 4 minutes after the administration of detomidine (20 μg/kg) and butorphanol (50 μg/kg). This period coincides with the maximum sedative effects of these drugs. The donkey was also being positioned in the stocks at this time and it is possible that the donkey slipped and was unable to stand up in the narrow crush. This donkey was in poor body condition and this may have played a role. The remainder of the procedure was performed without additional sedation after the detomidine was partially reversed with yohimbine. No other donkeys went down and the sedation and analgesia was found sufficient at the reduced doses. The dose of detomidine and butorphanol should be used with caution in patients with poor body condition scores.

The failure of detomidine to produce sufficient sedation in the equine is reported in the literature[10,11,12]. One donkey in the trial had the ability to kick accurately when stimulated with painful stimuli under detomidine sedation alone. The reaction of one donkey is of limited value but this should be born in mind when using this drug on its own. Very early on this trial, it became evident that the combination of detomidine and butorphanol produced better analgesia and sedation than detomidine alone. The pain and analgesic scores bear this out. It was for this reason that later in the trail when the detomidine alone failed that butorphanol was given. The superior sedation is the result of synergistic effects between detomidine and butorphanol.

The average length of sedation with detomidine alone was 20 minutes ± 10. This is of shorter duration that what has been reported in the literature for donkeys (35 minutes ± 4.01)[43]. In this trial, the donkeys under went surgical procedures and it is possible that the stress and adrenergic tone reduced the effective sedative time. The average length of sedation provided by the combination of detomidine and butorphanol was 67 minutes ± 19. This correlates with what has been reported in the equine literature.

The donkeys sedated with only detomidine still exhibited a deep pain response on the coronary band. They were only sedated for approximately 20 minutes. This makes a dose of 10μg/kg of detomidine alone insufficient for standing procedures in the donkey. Other

researches have shown that this dose produced poor analgesia with mild sedation in donkeys[43]. However, a dose of 10 μg/kg has been shown to be an effective sedative and analgesic in horses[11,12].

Cardiovascular Changes

After the intravenous injection of alpha$_2$ adrenergic agonists, the following cardiovascular effects have been described. Blood pressure initially increases rapidly due to direct stimulation of peripheral alpha$_1$ receptors[10 11 12 57]. This rise in blood pressure is the result of an increase in systemic vascular resistance, usually within two to five minutes after administration[10 11 12 56 57]. This is accompanied by a significant fall in heart rate due to a baroreceptor response[10 11 12 56 57]. The duration of the bradycardia is unpredictable[11 43]. After the hypertension, there is a centrally mediated drop in systemic vascular resistance and sympathetic tone and a more prolonged mild hypotension ensues[10 11 12 56]. The heart rate usually returns too normal with in a few minutes[12 57]. The cardiovascular side effects are dose dependent and reach their maximum effect 15 to 30 minutes after intravenous injection[12]. Central venous pressure and pulmonary capillary wedge pressure is not altered by detomidine in horses[56]. Cardiac output and tissue perfusion are reduced, although no clinical problems have been reported as a result of low tissue perfusion[11 12 43 56].

Heart rates decreased significantly over the first minute. This correlates well with what has been reported in equines given detomidine with or without butorphanol and with the one account of the use of detomidine in donkeys. This should coincide with the maximal increase in blood pressure associated with the direct stimulation of peripheral alpha$_1$ receptors[10 11 12 57]. After the initial drop, the heart rate did tend to return to base line values. It is well known that after the administration of alpha$_2$ adrenergic agonists the heart rate does tend to return to pre-treatment values. Usually this is with in 20-30 minutes. The donkeys were not acclimatised to the crush, as this would defeat the object of assessing the combination of drugs under field conditions. The stress of the new environment and handling of the animals during preparation may have increased the baseline heart rates due to an increase in sympathetic tone. The observation of both an atrioventricular and a sinoatrial block has been reported in the equine following the administration of these drugs[10 11 12]. Both these arrhythmias are well described after the use of alpha$_2$ adrenergic agonists and result from a decrease in sympathetic tone and an increase in parasympathetic tone.

Respiratory Changes

The respiratory changes are more interesting. Four donkeys showed abnormal respiratory rhythms. All these donkeys received butorphanol either initially or as part of an additional sedation. The rhythms are best described as short periods of tachypnoea followed a more prolonged bradypnoea. In some of the donkeys the tidal volume was initially large but this slowly tapered off at the end of the period of tachypnoea. This was diagnosed as a Cheyne-Stokes respiratory pattern. This pattern was recognised with the aid of capnography. The capnograph has been used to evaluate respiratory patterns with the sampling line in the ventral meatus of small animals[41]. The Cheyne-Stoke respiratory pattern is the result of altered functioning of the respiratory centres in the brain[22]. Hypoventilation results in a rise in the arterial partial pressure of carbon dioxide. The chemoreceptors perceive the increased partial pressure of carbon dioxide in the arterial blood and relay the information to the central nervous system to increase ventilation. The hyperventilation over-compensates for the raised carbon dioxide levels and the arterial partial pressure of carbon dioxide drops below normal. The chemoreceptors stop responding and apnoea follows[22]. Possible mechanisms included altered blood flow, desensitisation to peripheral chemoreceptors and central nervous system damage. Opioids have been reported to cause Cheyne-Stokes respiratory pattern[15].

Opioids and alpha$_2$ adrenergic agonists are known to depress ventilation and alter arterial partial pressures of carbon dioxide and oxygen. None of the donkeys showed any symptoms of intra- or post - operative hypoxia or respiratory failure. The possibility of hypoxia has been noted in the equine but this has never been found to be clinical significant. No blood gas analysis was done. No report in the literature to a Cheyne-Stokes respiratory pattern in horses in relation to detomidine and/or butorphanol could be found. The technique of the insertion of the capnograph into the ventral meatus has not been evaluated as an experimental tool. The use of tubing placed into the trachea has been evaulated[41]. The difference in respiratory gas composition between the ventral meatus of a nostril and the upper part of the trachea should be negligible. The nasal passageways humidify the air and it is quite possible that the inspiratory gases would not be completely humidified when analysed by the capnograph on inspiration. When the individual readings of respiratory rate are analysed for each donkey, the respiratory rate was very erratic between readings. In view of this, it is difficult to find any statistical difference in the respiratory rates. This explains the irregular nature of the respiratory graph.

Adverse Reactions

The diuresis induced by detomidine is associated with increased glomerular filtration rates, inhibition of anti-diuretic hormone release, inhibition of anti-diuretic hormone effect on the renal tubules and increased release of atrial natriuretic factor[12 16]. Two of the donkeys did void their bladders during or shortly after the procedure. This should be born in mind, especially when urogenital operations are planned.

Conclusion

Detomidine alone, at a dose of 10μg/kg, should not be used for moderate or severely painful procedures in donkeys without additional analgesia. A dose of 10 μg/kg of detomidine with 25 μg/kg of butorphanol was found effective for standing laproscopical procedures with minimal clinical side effects. Sedation and analgesia is expected to last approximately 60 minutes.

Chapter 7

Annexures

Annexe 1: Clinical Evaluation Form

Date: _____/_____/_____ Donkey No: _____

Body mass: _____ kg Temperature:__ °C

Heart Rate: _____ beats per minute Age: _____

Respiration: _____ breathes per minute

Haematology

RBC: _____ x 10^6/mm^3 PCV: _____ %

WBC: _____ x 10^3/mm^3

Lymphocytes: _____ % _____ x 10^3/mm^3

Monocytes: _____ % _____ x 10^3/mm^3

Eosinophilis: _____ % _____ x 10^3/mm^3

Basophilis: _____ % _____ x 10^3/mm^3

Neutrophils: _____ % _____ x 10^3/mm^3

Comments: _____

_____

_____

_____

_____

_____

_____

_____

_____

Annexe 2: Monitoring Form

Date: _____/_____/_____ Donkey No: _____

Onset of sedation time: _____

End of sedation time: _____

Time Mins	Heart Rate	Respiration Rate	Comments	Sedation		Pain		
				O	B	H	S	C
-5								
0								
1								
2								
3								
4								
5								
10								
15								
20								
30								
40								
50								
60								
70								
80								
90								
100								

O = Objective, B = Surgeons assessment, H = Head, S = Shoulders, C = Coronary Band.

Comments: _____

_____

_____

_____

_____

_____

_____

_____

Annexe 3: Doses of drugs given to donkeys

Donkey No:	Body mass	Detomidine (mg) 10µg/kg	Butorphanol (mg) 25µg/kg
1	168.00	1.68	4.20
8	146.00	1.46	3.65
25	122.00	1.22	3.05
31	120.00	1.20	3.00
20	164.00	1.64	4.10
22	126.00	1.26	3.15
11	90.00	0.90	2.25
3	180.00	1.80	4.50
14	162.00	1.62	4.05
9	136.00	1.36	3.40
Ave	141.40	1.41	3.54

Table 10: Calculated doses for donkeys – The dose of detomidine and butorphanol calculated for each donkey in mgs using the dose rate (mg/kg) given at the top of each column.

	Detomidine mls		Butorphanol mls	
Donkey No:	First dose	Add Dose	First dose	Add Dose
1	0.17			0.4
8	0.14	0.05		
25	0.12			
31	0.12			0.3
20	0.16			
22	0.12		0.3	
11	0.10		0.22	
3	0.18		0.45	
14	0.16		0.4	
9	0.14		0.68	
Ave mls	0.15	0.05	0.41	0.35
Ave ml/kg	0.001060	0.000342	0.002953	0.002430

Table 11: Actual doses of drugs given to donkeys in millilitres – This is the recorded volume of each drug given. The "first dose" column indicates the quantity of drug given at Time 0. Any additional doses of detomidine and butorphanol were recorded in the "add dose" column. Blank spaces indicate that the drug was not given. The concentration of detomidine is 10 mg/ml and that butorphanol is 50 mg/ml.

	Detomidine mgs		Butorphanol mgs	
Donkey No:	First dose	Add Dose	First dose	Add Dose
1	1.70			4.00
8	1.40	0.50		
25	1.20			
31	1.20			3.00
20	1.60			
22	1.20		3.00	
11	1.00		2.20	
3	1.80		4.50	
14	1.60		4.00	
9	1.40		6.80	
Ave	1.54	0.50	4.10	3.50
Ave mg/kg	0.01089	0.003424	0.02953	0.01215

Table 12: Dose of drugs given to donkeys in milligrams – The volume of drug given was multiplied by the concentration to give the dose in milligrams. The "first dose" column indicates the quantity of drug given at Time 0. Any additional doses of detomidine and butorphanol were recorded in the "add dose" column. Blank spaces indicate that the drug was not given. The milligram dose was then divided by the mass of the donkey to give the dose rate (mg/kg). This was then compared to Table 10.

Annexe 4: Haematological values for donkeys

Parameter	Zinkl et al[63]	Fowler[19]
Hb (g/l)	13.1	13.25
RCC (x10^12/l)	6.65	5.02
Ht (l/l)	38	0.366
MCV (fl)	57.9	74.85
MCHC (g/dl cells)	34.3	35.49
WCC (x10^9/l)	10.3	8.963
Ab N(mat) (x10^9/l)	4.7	4.766
Ab N(immat) (x10^9/l)	0.010	-
Ab Lymp (x10^9/l)	4.4	3.560
Ab Mono (x10^9/l)	0.510	0.206
Ab Eos (x10^9/l)	0.580	0.494
Ab Baso (x10^9/l)	0.04	0.005
Platelets (x10^9/l)	330	-

Table 13: Normal Haematological Values for donkeys – The average of these two authors were used for comparisons.

Donkey No:	1	2	3	4	8	9	11	14	20	22	25	31
Hb (g/l)	141	117	140	123	119	140	133	94	135	109	50	104
RCC (x10^12/l)	7.54	6.66	7.69	7.09	5.89	6.91	7.19	4.43	7.09	5.35	2.41	5.96
Ht (l/l)	0.38	0.32	0.39	0.34	0.32	0.38	0.38	0.26	0.37	0.3	0.13	0.29
MCV (fl)	50.9	48.1	50.2	47.6	54.3	55	52.5	58.1	52.2	55.6	55.4	48.3
MCHC (g/dl cells)	36.6	36.6	36.4	36.4	37.1	36.8	35.2	36.6	36.6	36.7	37.9	36
RDW %	24	22.9	22.6	23.9	20.7	22.8	21.9	19.9	22.3	19.5	21.1	24.4
WCC (x10^9/l)	8.1	9.8	14.8	8.5	12.8	7.5	8.9	6.5	8.8	14.8	12.6	10.3
Ab N(mat) (x10^9/l)	3.73	3.72	7.84	3.4	6.4	4.57	4.18	3.51	5.98	7.1	7.56	3.3
Ab N(immat) (x10^9/l)	0.16	0	0	0	0.13	0	0	0	0	0	0.38	0
Ab Lymp (x10^9/l)	2.59	4.12	2.81	3.57	4.35	2.1	4	2.21	1.94	5.92	3.78	5.77
Ab Mono (x10^9/l)	1.3	1.76	0.59	0.77	0.38	0.6	0.53	0.26	0.53	1.18	0.88	0.52
Ab Eos (x10^9/l)	0.24	0.2	3.4	0.77	1.28	0.23	0.18	0.52	0.35	0.59	0	0.62
Ab Baso (x10^9/l)	0.08	0	0.15	0	0.13	0	0	0	0	0	0	0.1
Thr C (x10^9/l)	238	215	334	215	261	264	214	149	265	185	136	257
MPV (fl)	6.37	5.17	5.44	5.22	6.55	5.18	6.13	5.47	5.59	5.39	5.86	5.97
Ansio	3+	3+	3+	3+	3+	3+	4+	1+	2+	4+	1+	3+
HJB	1+		1+	1+	1+		1+			1+	2+	
L Blasts	1+	2+	1+	1+	1+	1+	1+		1+	1+	2+	
M Blasts	2+	2+	1+	2+	1+	1+	3+			1+	2+	
M Active	4+	2+	1+	2+	1+	2+	2+	1+	1+	1+	4+	3+
Parasites	N	N	N	N	N	N	B.eq	N	N	N	B.eq	B.eq

Table 14: Haematology Results for the donkeys – The individual haematological results for each donkey are presented.

Annexe 5: Physiological Data

Donkey No:	1	8	25	31	20	Mean	22	11	3	14	9	Mean
Time:			Detomidine						Detomidine-Butorphanol			
-5	51	42	50	63	65	54.2	52	38	53	49	38	46
0	48	41	56	65	52	52.4	42	48	54	42	37	44.6
1	38	31	42	50	31	38.4	27	37	32	33	18	29.4
2	45	36	43	50	33	41.4	26	39	29	32	31	31.4
3	47	34	38	49	37	41	28	40	30	33	32	32.6
4	46	32	42	43	36	39.8	28	41	30	33	30	32.4
5	38	33	40	41	38	38	27	41	30	35	28	32.2
10	41	29	45	43	38	39.2	29	54	30	30	32	35
15	43	28	42	39	37	37.8	32	51	37	32	36	37.6
20	43	29	45	44	39	40	30	47	36	31	33	35.4
30	42	30	48	21	37	35.6	30	46	39	34	31	36
40	41	27			48	38.6	33	45	34	40	30	36.4
50	43	28			51	40.6			36		35	35.5
60	41	32				36.5			35		34	34.5
70		28				28						
80		30				30						

Table 15: Heart Rate Data – The heart rate for each donkey at each time interval is given. The table is divided vertically into two groups. The average heart rate for each group is given in the last column.

Donkey No:	1	8	25	31	20	Ave	22	11	3	14	9	Ave
Time:				Detomidine						Detomidine-Butorphanol		
-5	24	18	10	24	36	22.4	14	12	15	13	20	14.8
0	18	18	11	27	40	22.8	10	18	36	10	22	19.2
1	12	18	13	21	42	21.2	18	12	18	11	18	15.4
2	12	20	8	10	36	17.2	18	20	18	7	18	16.2
3	12	24	7	18	30	18.2	12	18	21	11	18	16
4	12	24	8	19	36	19.8	12	24	21	11	18	17.2
5	12	20	9	15	36	18.4	12	18	29	29	20	21.6
10	18	18	10	9	42	19.4	12	30	24	14	16	19.2
15	12	16	9	26	24	17.4	11	36	22	12	16	19.4
20	60	14	10	29	24	27.4	12	30	22	14	18	19.2
30	48	12	8	34	24	25.2	12	32	27	12	22	21
40	24	12			24	20	12	24	23	17	20	19.2
50	42	10			30	27.3	12		23		24	19.6
60	42	12				27			20			20
70		11				11						
80		12				12						

Table 16: Respiratory Data – The respiratory rate for each donkey at each time interval is given. The table is divided vertically into two groups. The average respiratory rate for each group is given in the last column.

Annexe 6: Sedative and Analgesic Data

Donkey No:	1	8	25	31	20	Mode	22	11	3	14	9	Mode
Time:	Detomidine						Detomidine-Butorphanol					
0	0	0	0	0	0	0	0	0	0	0	0	0
5	1	3	3	2	3	3	3	3	3	3	3	3
10	1	3	3	2	3	3	3	3	3	3	3	3
15	1	2	2		2	2	3	3	3	3	3	3
20		1	1		2	1	3	3	2	3	3	3
30			1		1	1	3	3	2	3	3	3
40					0	0	3	3	2	2	2	2
50					0	0			2		2	2
60									2		2	2
70												
80												

Table 17a: Sedative Scores – This table presents the sedative scores for each donkey as described in Table 5. This Table shows the results after the initial intravenous administration. The mode score for each group is given in the last column and is plotted in Figure 2. Blank spaces indicate that no further recording were made as either the procedure was completed or additional sedation or analgesia was required.

Donkey No:	1	8	25	31	20	Mode
Time:	Detomidine					
0						
5						
10						
15				3		3
20	3			3		3
30	3	3		3		3
40	3	3				3
50	3	2				2
60	3	2				2
70		1				1
80		1				1

Notes:1,31Received butorphanol
8 Received detomidine

Table 17b: This table shows the sedation scores for the detomidine group after additional analgesics or sedatives were given. Only the detomidine group received additional doses.

Histogram		
Score	D	DB
0	2	0
1	7	0
2	6	9
3	6	25

D = Detomidine, DB = Detomidine-Butorphanol

Table 17c: This table shows a histogram of the sedatives scores as obtained in Table 17a. The histogram is plotted in Figure 3.

Donkey No:	1	8	25	31	20	Mode	22	11	3	14	9	Mode
Time:			Detomidine						Detomidine-Butorphanol			
0	0	0	0	0	0	0	0	0	0	0	0	0
5	2	0	2	2	3	2	3	2	2	3	3	3
10	1	1	2	1	2	1	3	3	3	3	3	3
15	1	2	2		2	2	3	3	3	3	3	3
20		2	2		2	2	3	3	3	3	3	3
30			0		2	2	3	3	3	3	3	3
40					1	1	3	3	3	3	3	3
50					1	1			3		2	2
60									3		2	2
70												
80												

Table 18a: Analgesic Scores – Head - This table present the analgesic scores for each donkey as described in Table 6. This Table shows the results after the initial intravenous administration. The mode score for each group is given in the last column and is plotted in Figure 5. Blank spaces indicate that no further recording were made as either the procedure was completed or additional sedation or analgesia was required.

Donkey No:	1	8	25	31	20	Mode
Time:			Detomidine			
0						
5						
10						
15				2		2
20	2			3		3
30	2	1		3		2
40	2	2				2
50	2	2				2
60	2	2				2
70		2				2
80		2				2

Notes: 1,31 Received butorphanol
8 Received detomidine

Table 18b: This table shows the analgesic scores for the detomidine group after additional analgesics or sedatives were given. Only the detomidine group received additional doses.

Histogram		
Score	D	DB
0	2	0
1	6	0
2	12	4
3	1	30

D = Detomidine, DB = Detomidine-Butorphanol

Table 18c: This table shows a histogram of the analgesic scores as obtained in Table 18a. The histogram is plotted in Figure 8.

Donkey No:	1	8	25	31	20	Mode	22	11	3	14	9	Mode
Time:	Detomidine						Detomidine-Butorphanol					
0	0	0	0	0	0	0	0	0	0	0	0	0
5	2	0	2	2	3	2	3	3	3	3	3	3
10	1	1	2	1	2	1	3	3	3	3	3	3
15	1	2	2		2	2	3	3	3	3	3	3
20		2	2		2	2	3	3	3	3	3	3
30			1		2	1	3	3	3	3	3	3
40					1	1	3	3	3	3	3	3
50					1	1			3		2	2
60									2		2	2
70												
80												

Table 19a: Analgesic Scores – Shoulder – This table presents the analgesic scores for each donkey as described in Table 6. This table shows the results after the initial intravenous administration. The mode score for each group is given in the last column and is plotted in Figure 5. Blank spaces indicate that no further recording were made as either the procedure was completed or additional sedation or analgesia was required.

Donkey No:	1	8	25	31	20	Mode
Time:	Detomidine					
0						
5						
10						
15				2		2
20	2			3		2
30	2	1		3		2
40	2	2				2
50	2	2				2
60	2	2				2
70		2				2
80		2				2

Notes: 1,31 Received butorphanol
8 Received detomidine

Table 19b: This table shows the analgesic scores for the detomidine group after additional analgesics or sedatives were given. Only the detomidine group received additional doses.

	Histogram	
Score	D	DB
0	1	0
1	7	0
2	12	3
3	1	31

D = Detomidine, DB = Detomidine-Butorphanol

Table 19c: This table shows a histogram of the analgesic scores as obtained in Table 19a. The histogram is plotted in Figure 9.

Donkey No:	1	8	25	31	20	Mode	22	11	3	14	9	Mode
Time:	Detomidine						Detomidine-Butorphanol					
0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	2	1	1	2	2	2
10	0	1	0	0	0	0	2	1	1	2	2	2
15	0	2	0		0	0	2	1	1	1	2	1
20		2	0		0	0	1	1	1	1	1	1
30		1	0		0	0	1	1	1	1	1	1
40					0	0	1	1	1	1	1	1
50					0	0			1		1	1
60									0		0	0
70												
80												

Table 20a: Analgesic Score – Coronary Band – These tables presents the analgesic scores for each donkey as described in Table 6. This table shows the results after the initial intravenous administration. The mode score for each group is given in the last column and is plotted in Figure 7. Blank spaces indicate that no further recording were made as either the procedure was completed or additional sedation or analgesia was required.

Donkey No:	1	8	25	31	20	Mode
Time:	Detomidine					
0						
5						
10						
15				1		1
20	1			1		1
30	1	1		1		1
40	1	2				2
50	1	2				2
60	1	2				2
70		1				1
80		1				1

Notes: 1,31 Received butorphanol
8 Received detomidine

Table 20b: This table shows the analgesic scores for the detomidine group after an additional analgesics or sedatives were given. Only the detomidine group received additional doses.

Histogram		
Score	D	DB
0	18	2
1	2	24
2	2	8
3	0	0

D = Detomidine, DB = Detomidine-Butorphanol

Table 20c: This table shows a histogram of the analgesic scores as obtained in Table 20a. The histogram is plotted in Figure 10.

Annexe 7: Graphical Data

Unless otherwise indicated, Group D is plotted as a white block with edges and Group DB is plotted as a black block with black edges. Time is on the X axis and plotted in terms of time intervals as data was recorded.

Figure 1: Sedation Score Bar Graph – Mode Values

Mode values for sedation scores have been plotted for each time interval. No difference in mode values occurs until the 10 minute time interval. Group DB maintains a mode score of 3 until the 30 minute time interval. Group D has a mode of score 0 at the 40 minute interval.

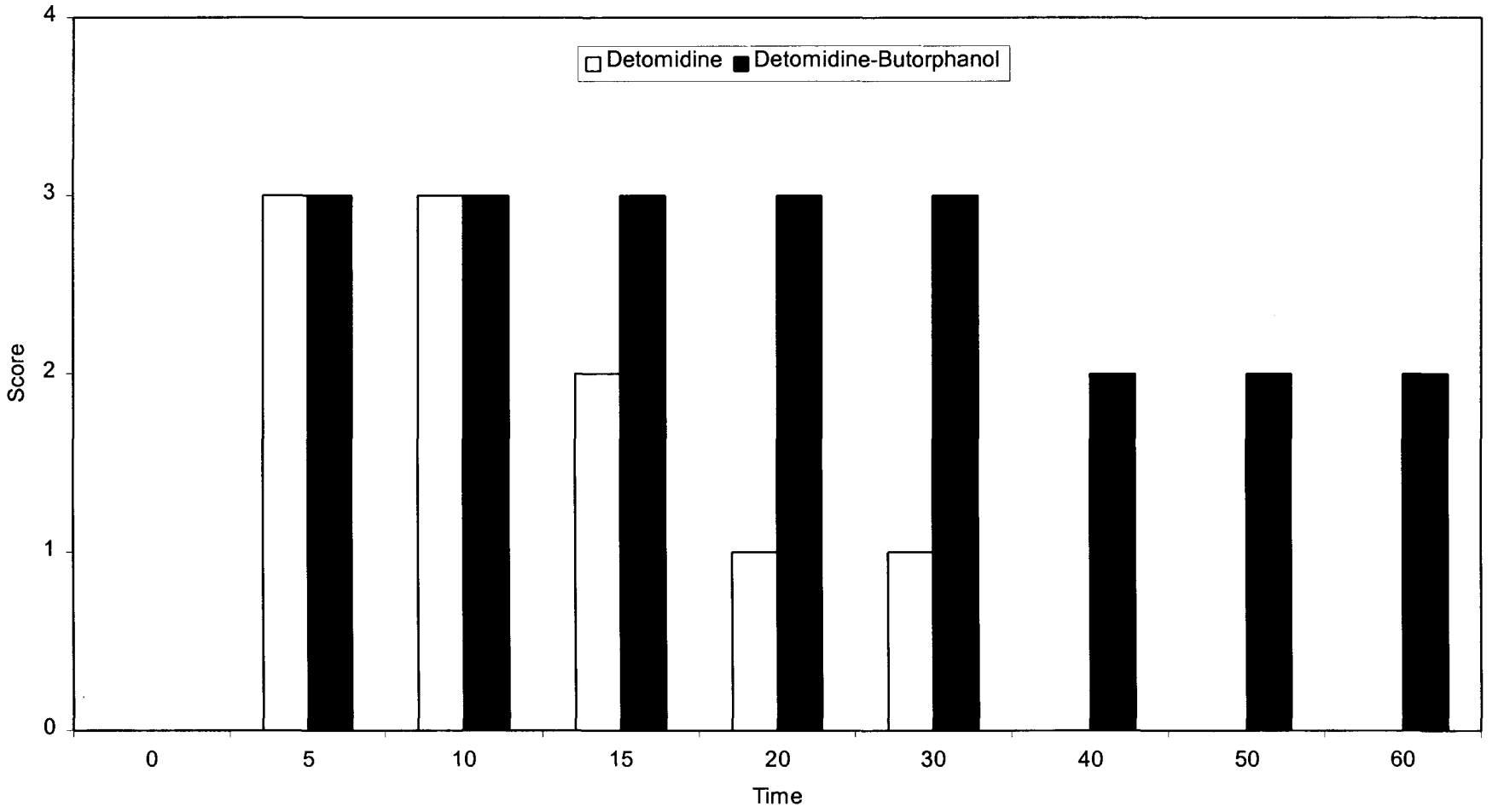


Figure 2: Sedative Score Bar Graph – Mean Scores

The mean value for the sedation score have been plotted for each time interval. The difference between Group DB and Group D is apparent from the 5 minute time interval. Group D has a mean score of 0 at the 40 minute time interval. Group DB has mean score greater then 2 at 60 minutes.

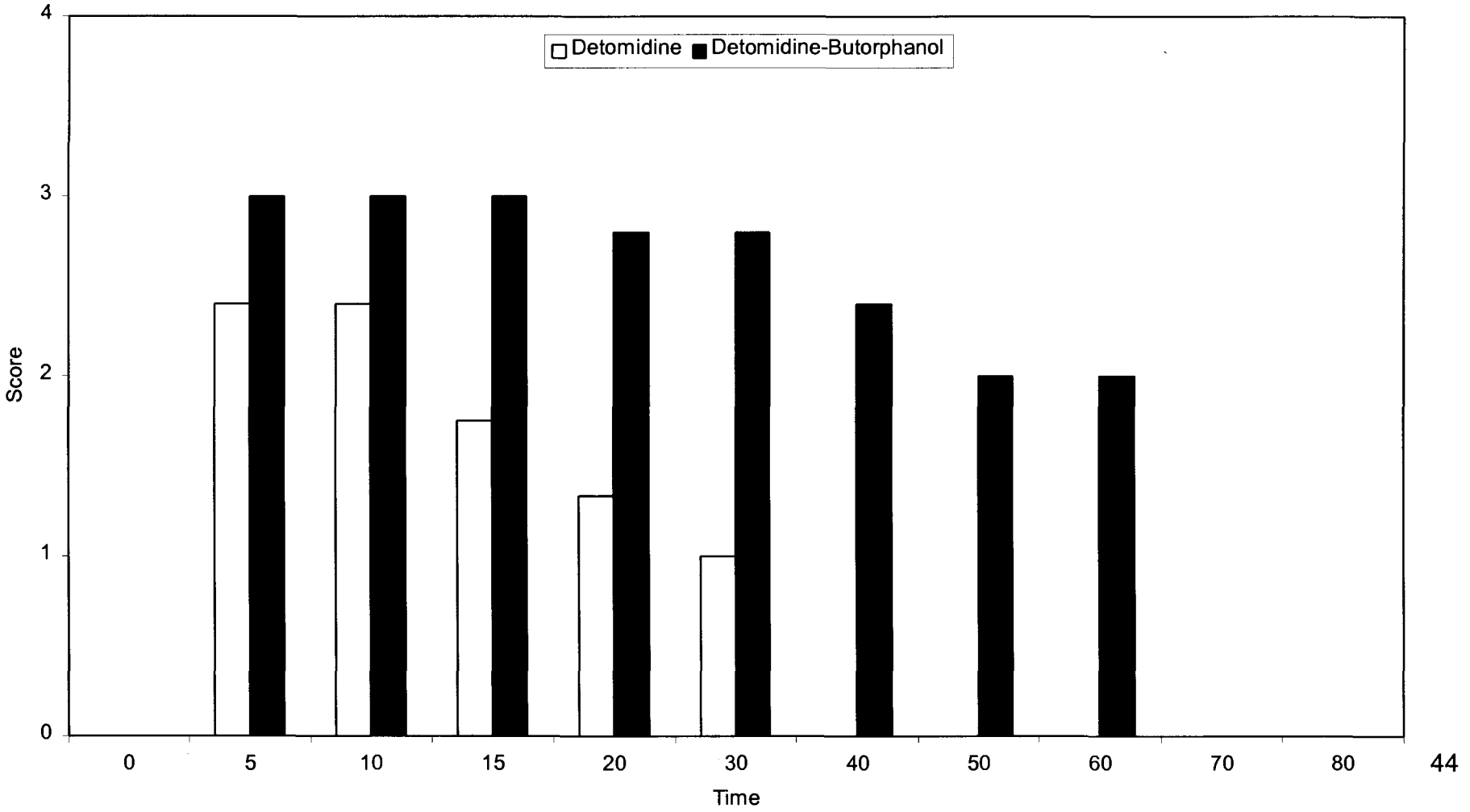


Figure 3: Sedative Scores Bar Graph - Histogram

The frequency of each sedative score for each group is plotted. The frequency is determined over the full 80 minute observational period. Group DB has score of 2 or more for the entire observational period.

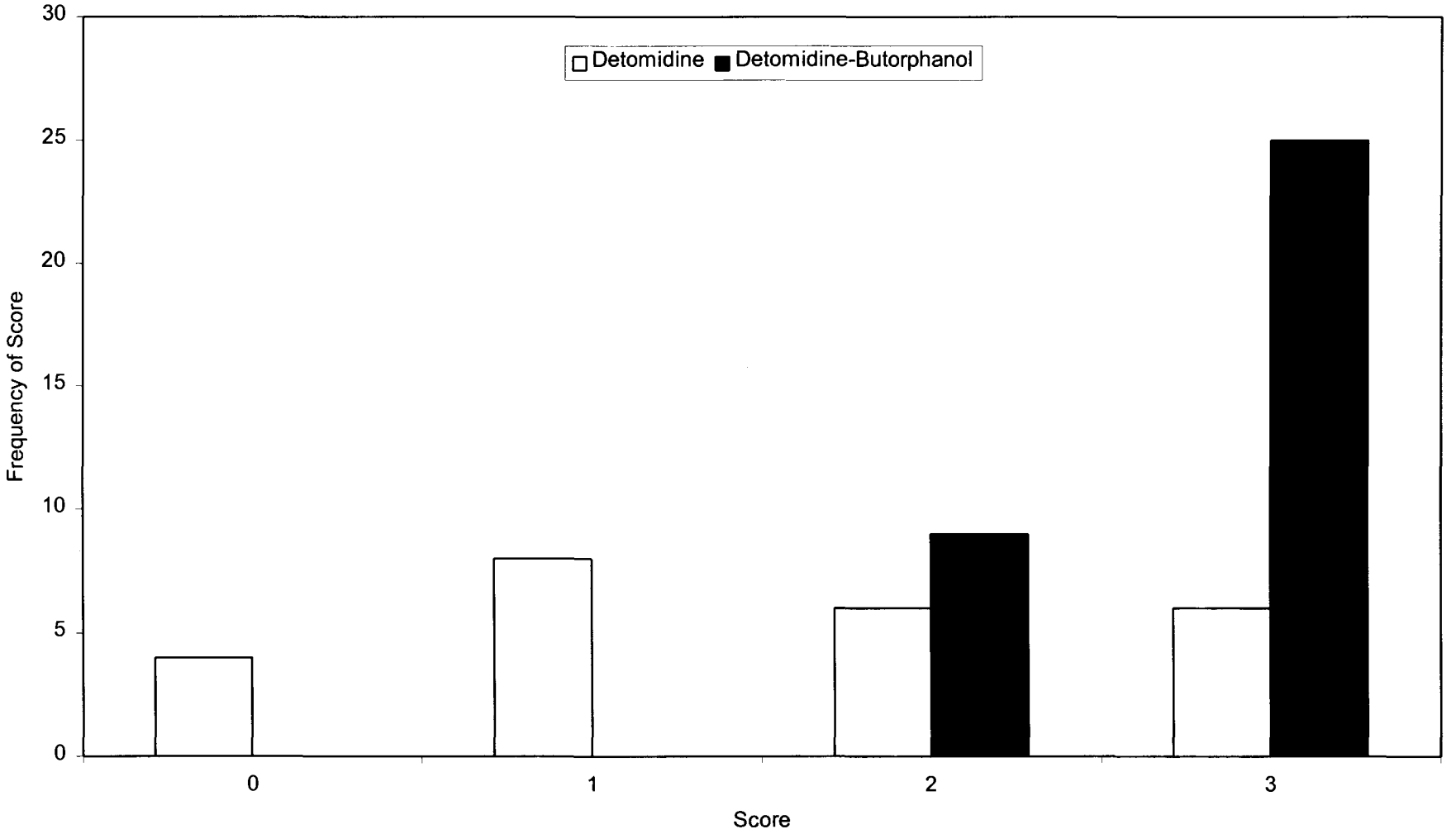


Figure 4: Sedation Scores Bar Graph - Added Values

The sum of sedative scores for each time interval has been added and plotted against time. A maximum score of 15 attainable for each group at every time interval. The difference between Group D and Group DB is particularly obvious from the 15 minute time interval.

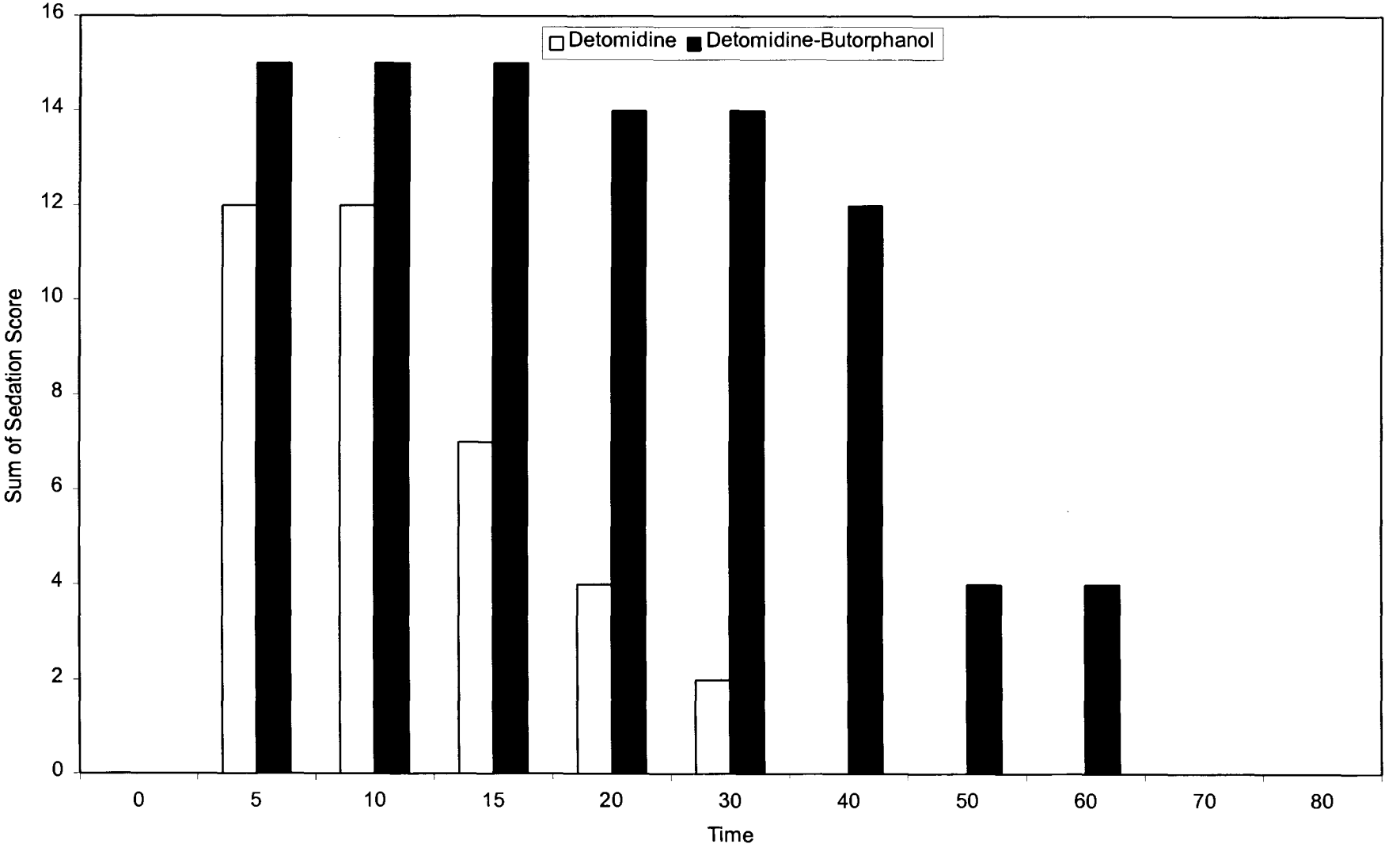


Figure 5: Pain Scores Bar Graph – Mode Values - Head

Mode values for pain scores conducted around the head for each time interval have been plotted. The difference between Group D and Group DB is evident but not obvious.

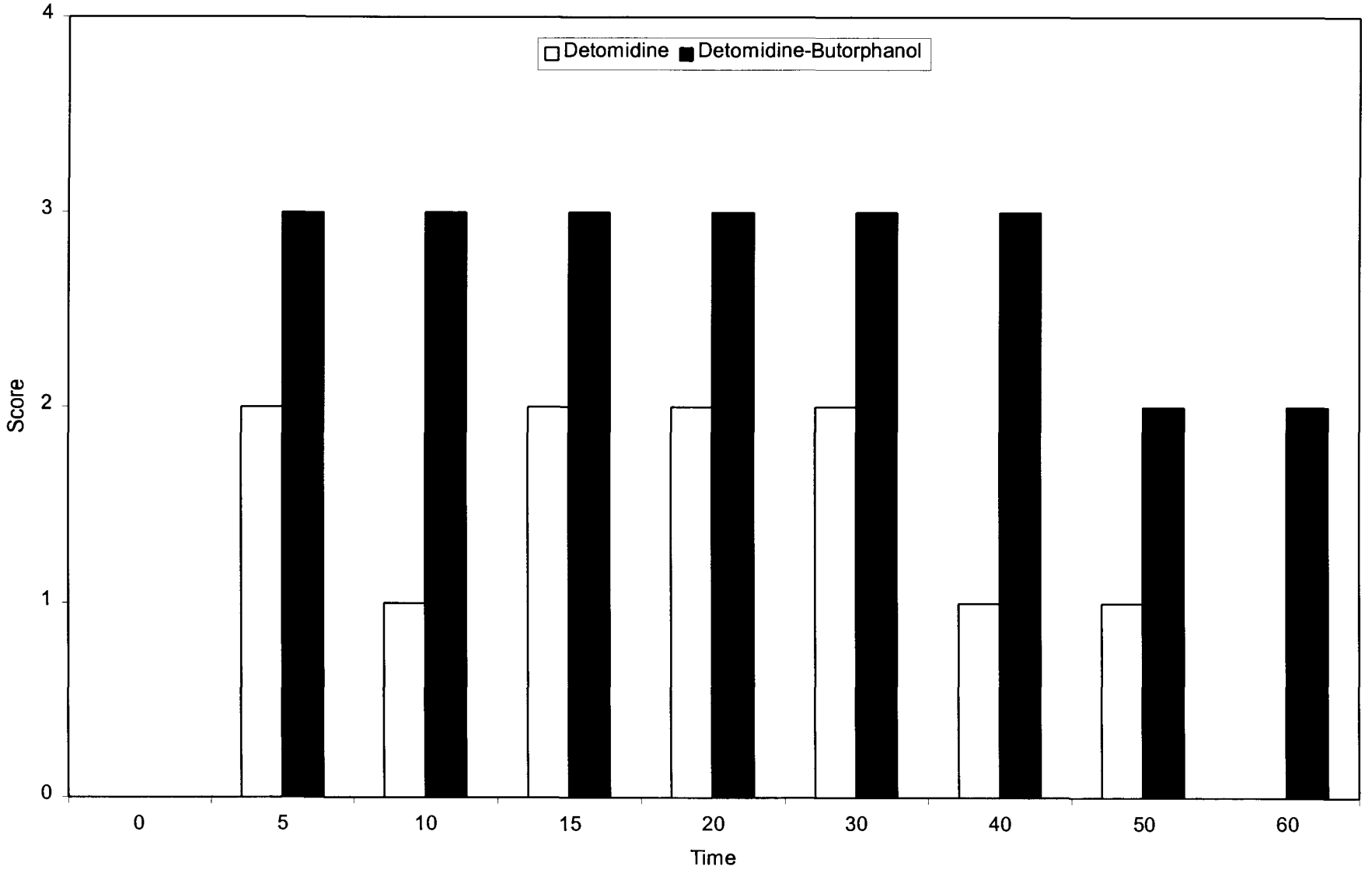


Figure 6: Pain Scores Bar Graph - Mode Graph - Shoulder

Mode values for pain scores conducted around the shoulder for each time interval have been plotted. The difference between Group D and Group DB is evident but not obvious. This graph has a similar profile to Figure 6.

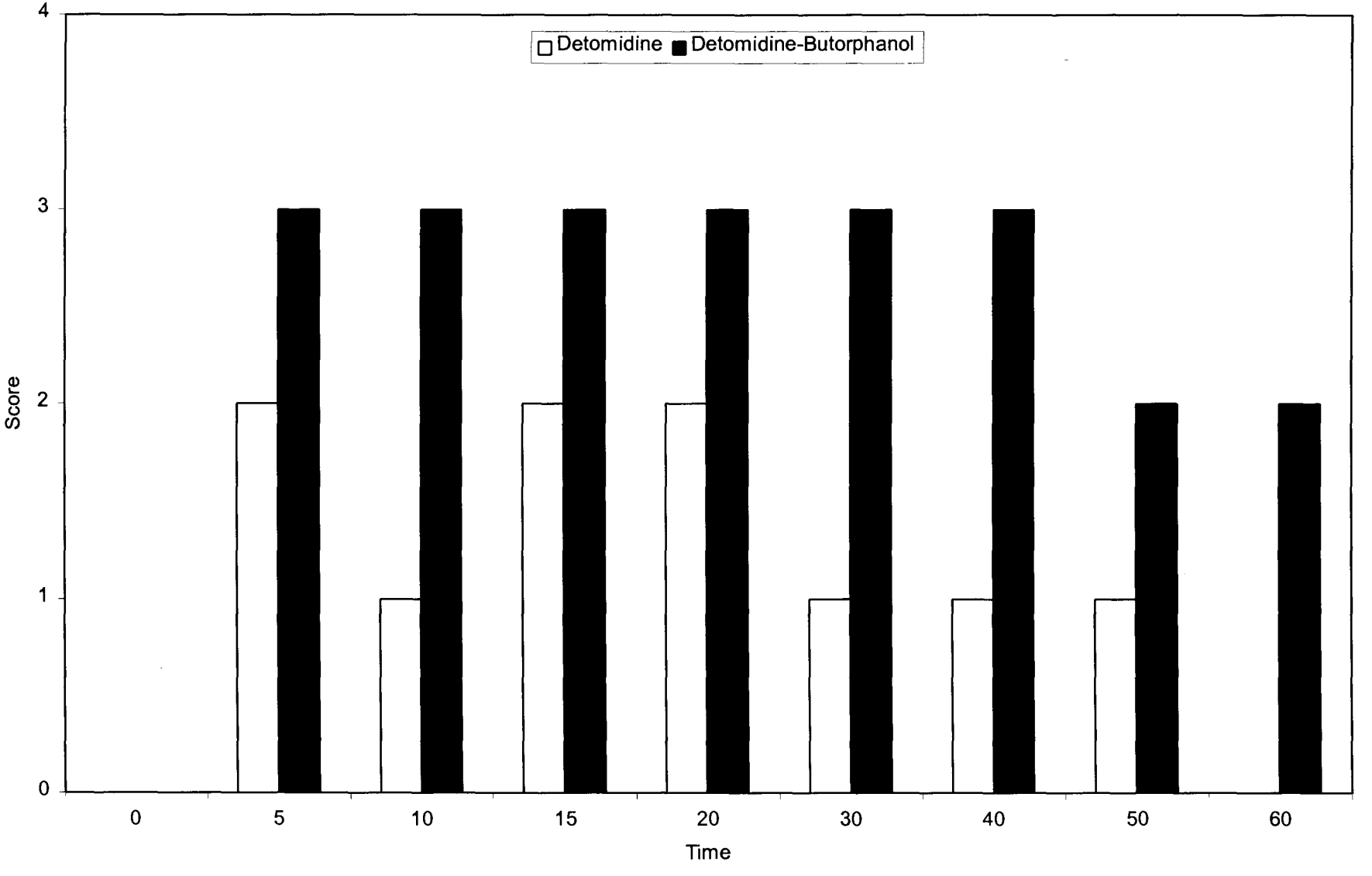


Figure 7: Pain Scores Bar Graph - Mode Graph - Coronary Band

Mode values for pain scores conducted around the coronary band for each time interval have been plotted. The difference between Group D and Group DB is obvious as in Group D coronary band pain was never abolished.

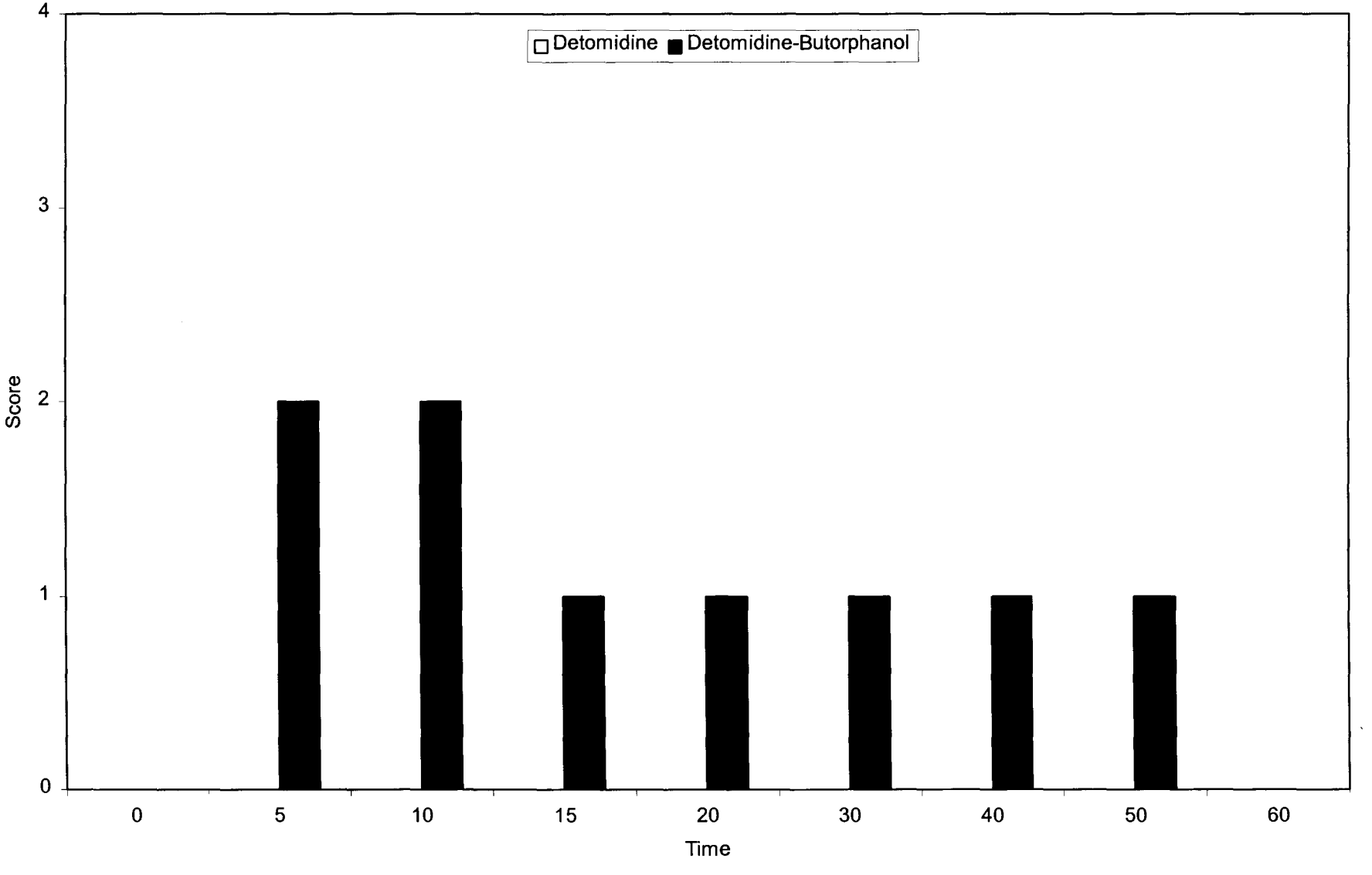


Figure 8: Pain Score Bar Graph - Histogram - Head

The frequency of each pain score for each group has been plotted. The frequency is determined from the first 60 minutes of the observational period. Group DB has a very high frequency 3 score values.

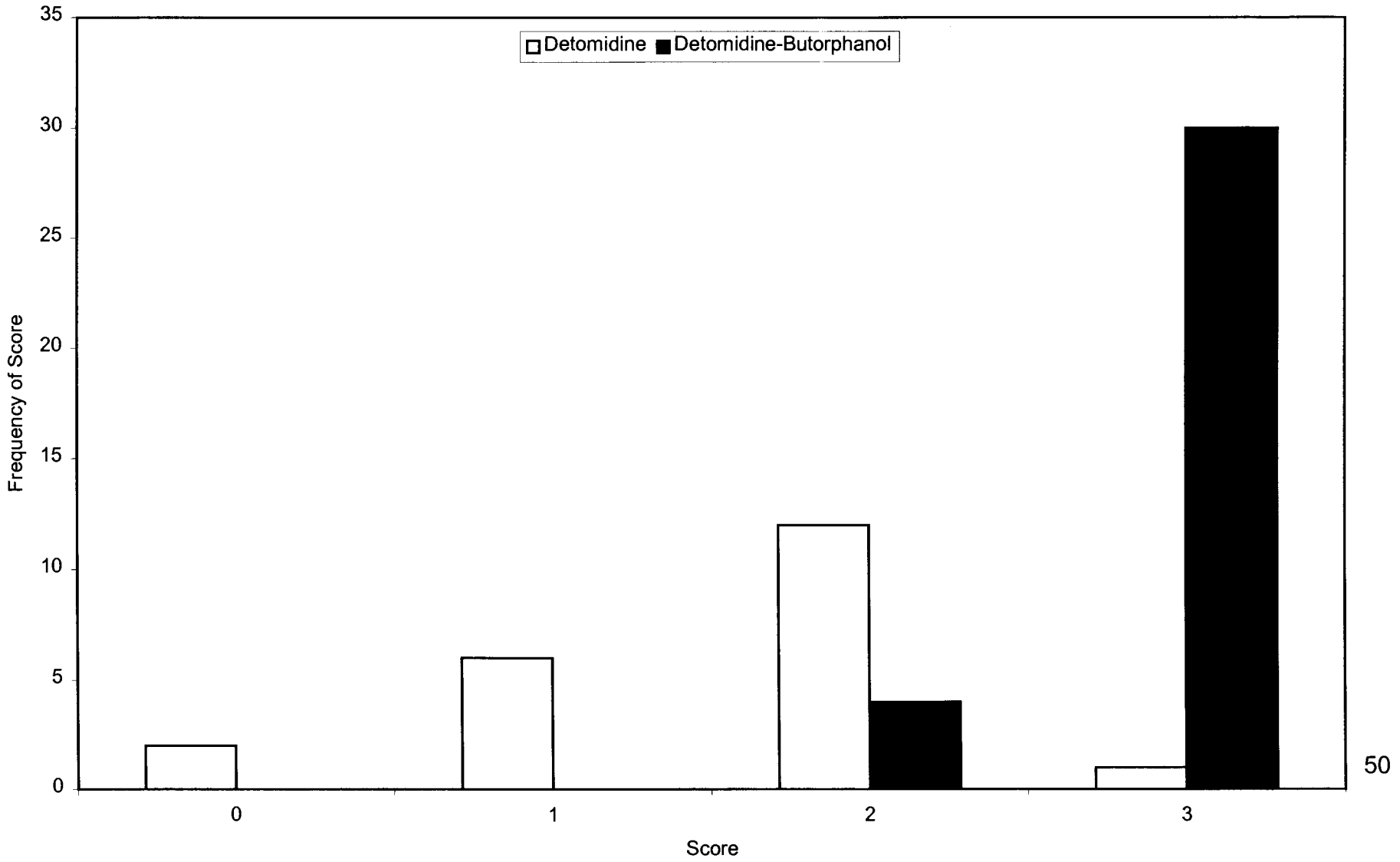


Figure 9: Pain Score Bar Graph - Histogram- Shoulder

The frequency of each pain score for each group has been plotted. The frequency is determined from the first 60 minutes of the observational period. Group DB has a very high frequency 3 score values. This graph is identical to Figure 8.

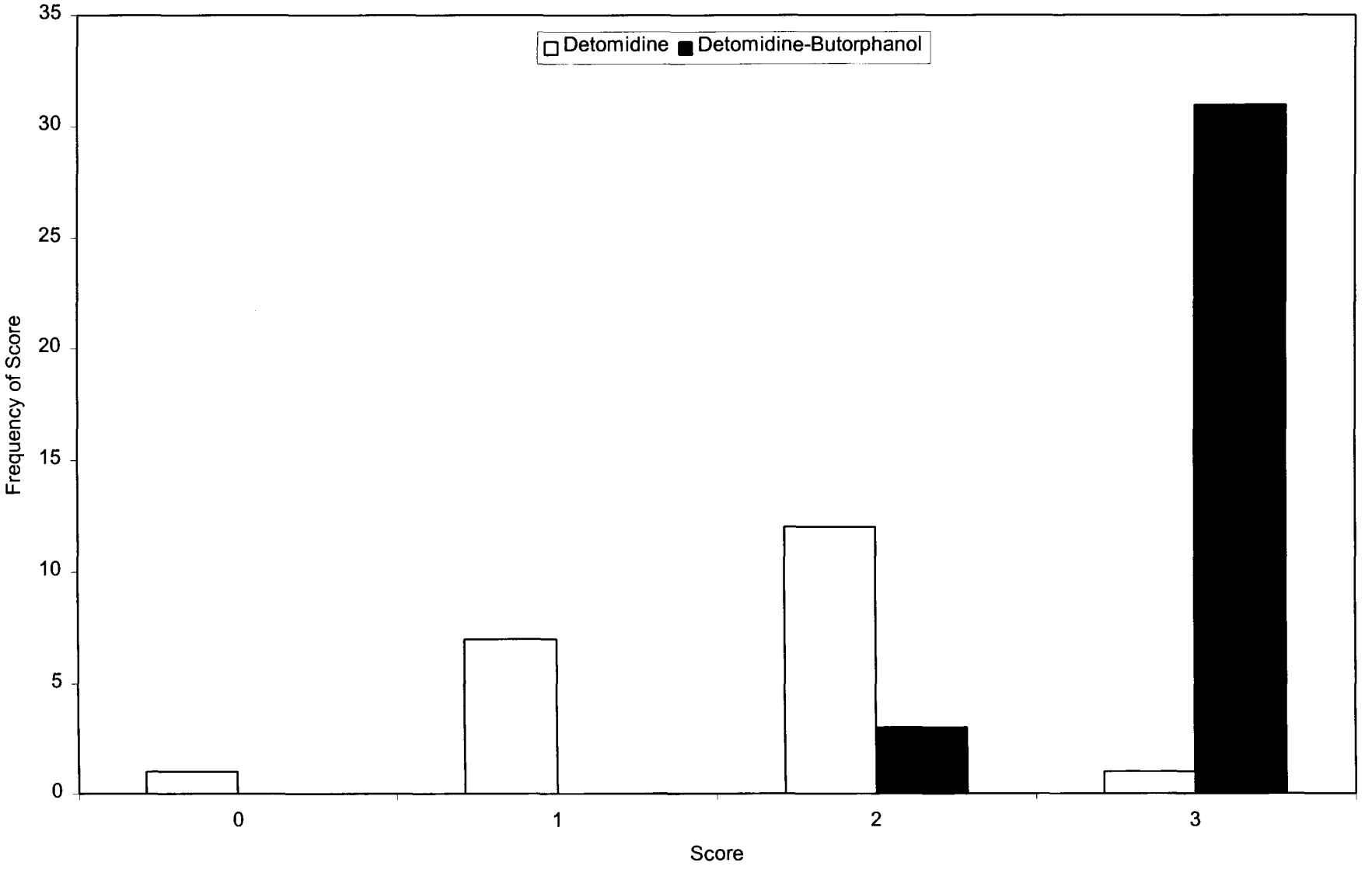


Figure 10: Pain Score Bar Graph – Histogram - Coronary Band

The frequency of each pain score for each group has been plotted. The frequency is determined from the first 60 minutes of the observational period. Group DB has a very high distribution of 1 score values while Group D has a distribution of 0 score values.

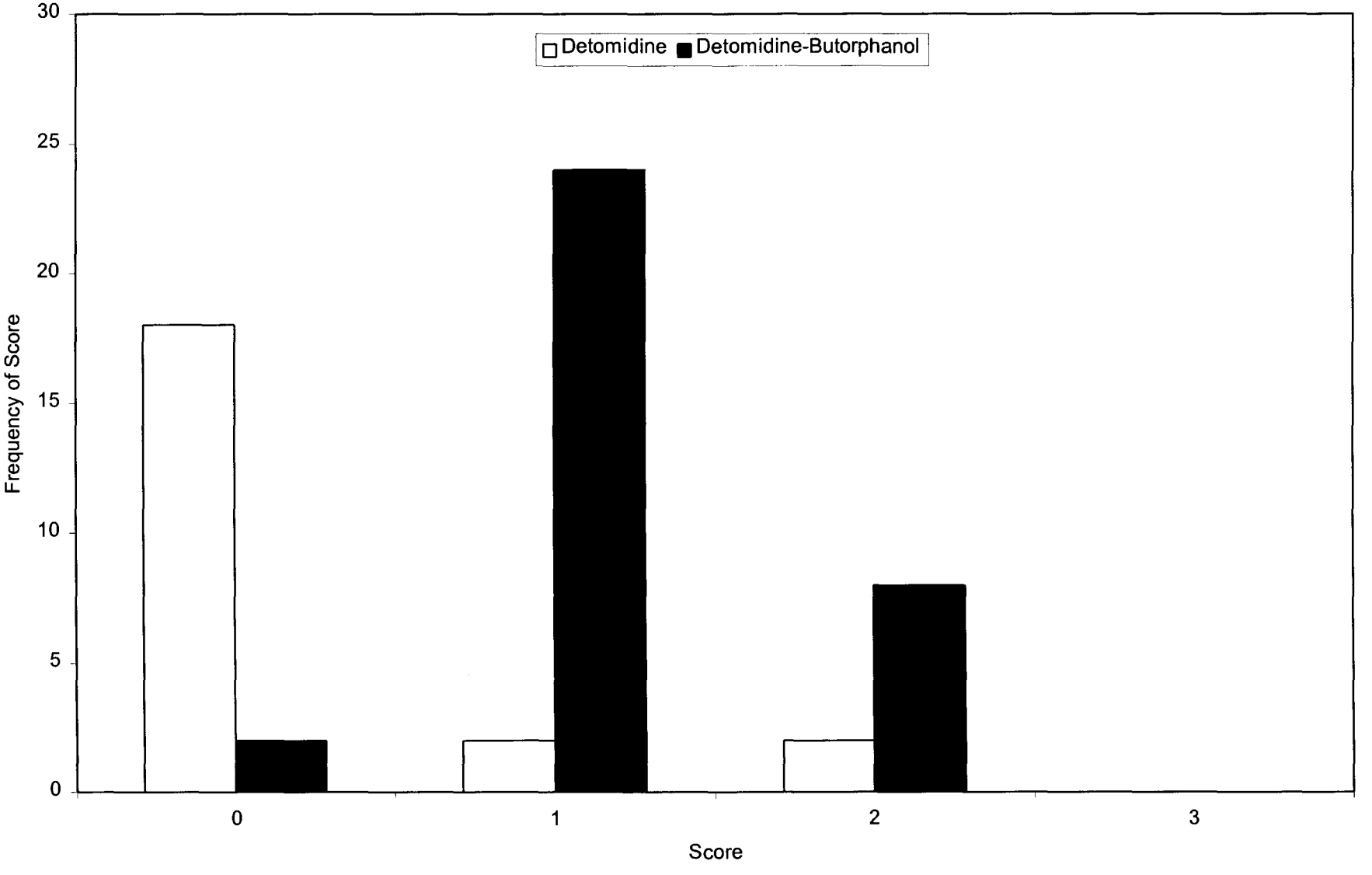


Figure 11: Pain Scores Bar Graph – Added Values - Head

The sum of pain scores for each time interval has been added and plotted against time. A maximum score of 15 is attainable for each group at every time interval. The difference between Group D and Group DB is particularly obvious from the 10 minute time interval.

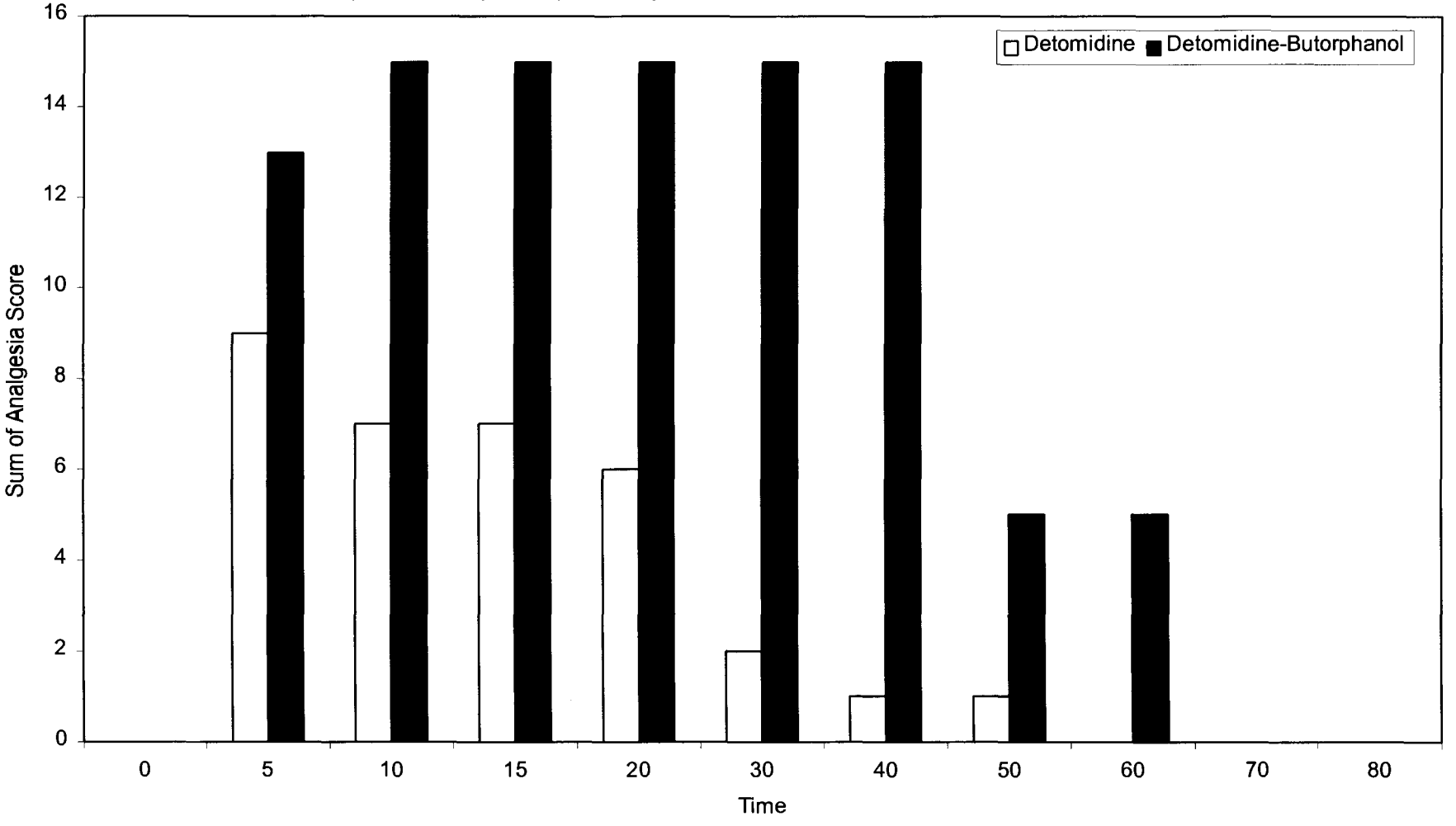


Figure 12: Pain Scores Bar Graph – Added Values - Shoulder

The sum of pain scores for each time interval has been added and plotted against time. A maximum score of 15 is attainable for each group at every time interval. The difference between Group D and Group DB is particularly obvious from the 10 minute time interval. This graph has a similar profile to Figure 11.

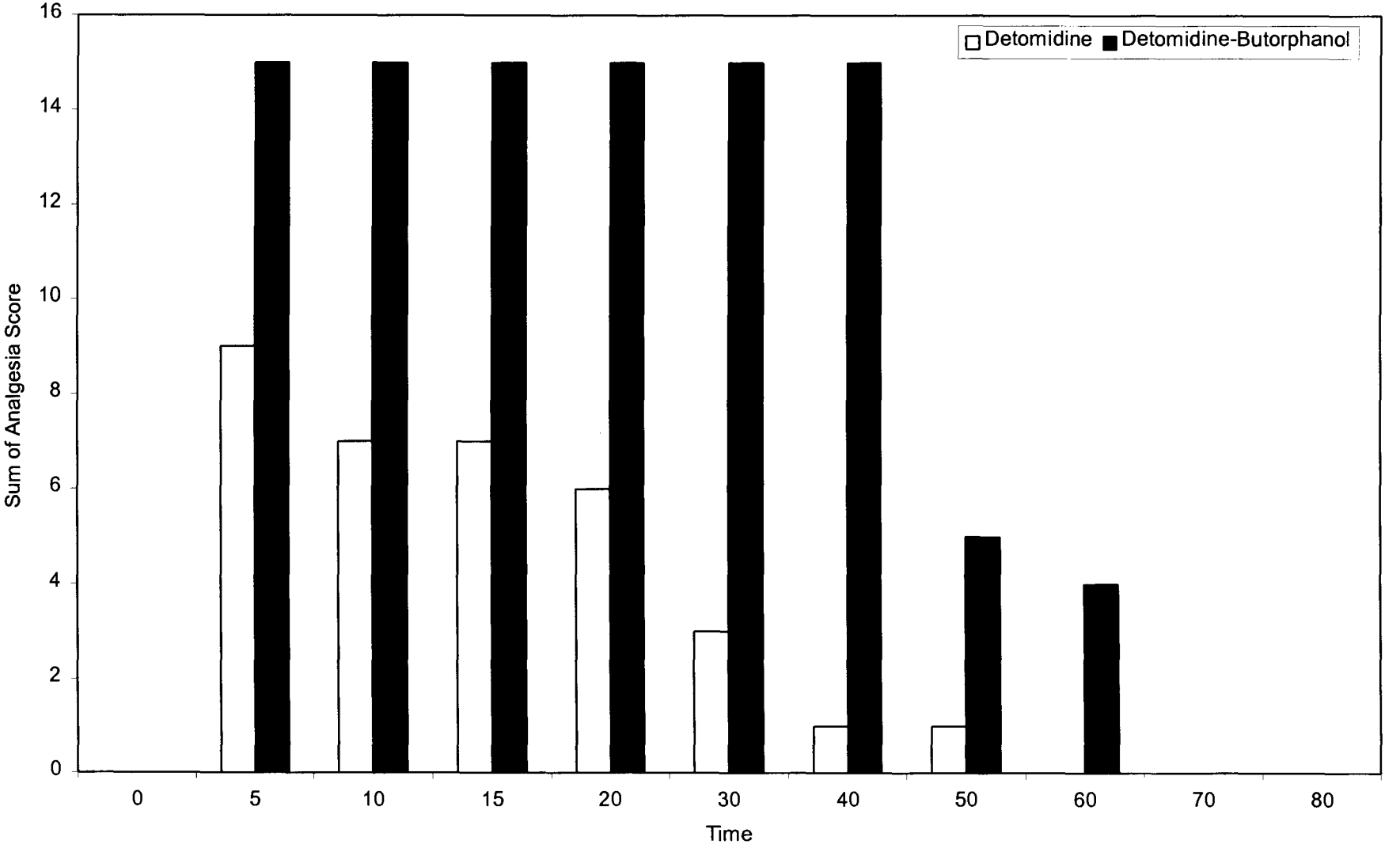


Figure 13: Pain Scores Bar Graph – Added Values - Coronary Band

The sum of pain scores for each time interval has been added and plotted against time. A maximum score of 15 is attainable for each group at every time interval. Neither Group scored the maximum available however Group DB performed considerably better then Group D.

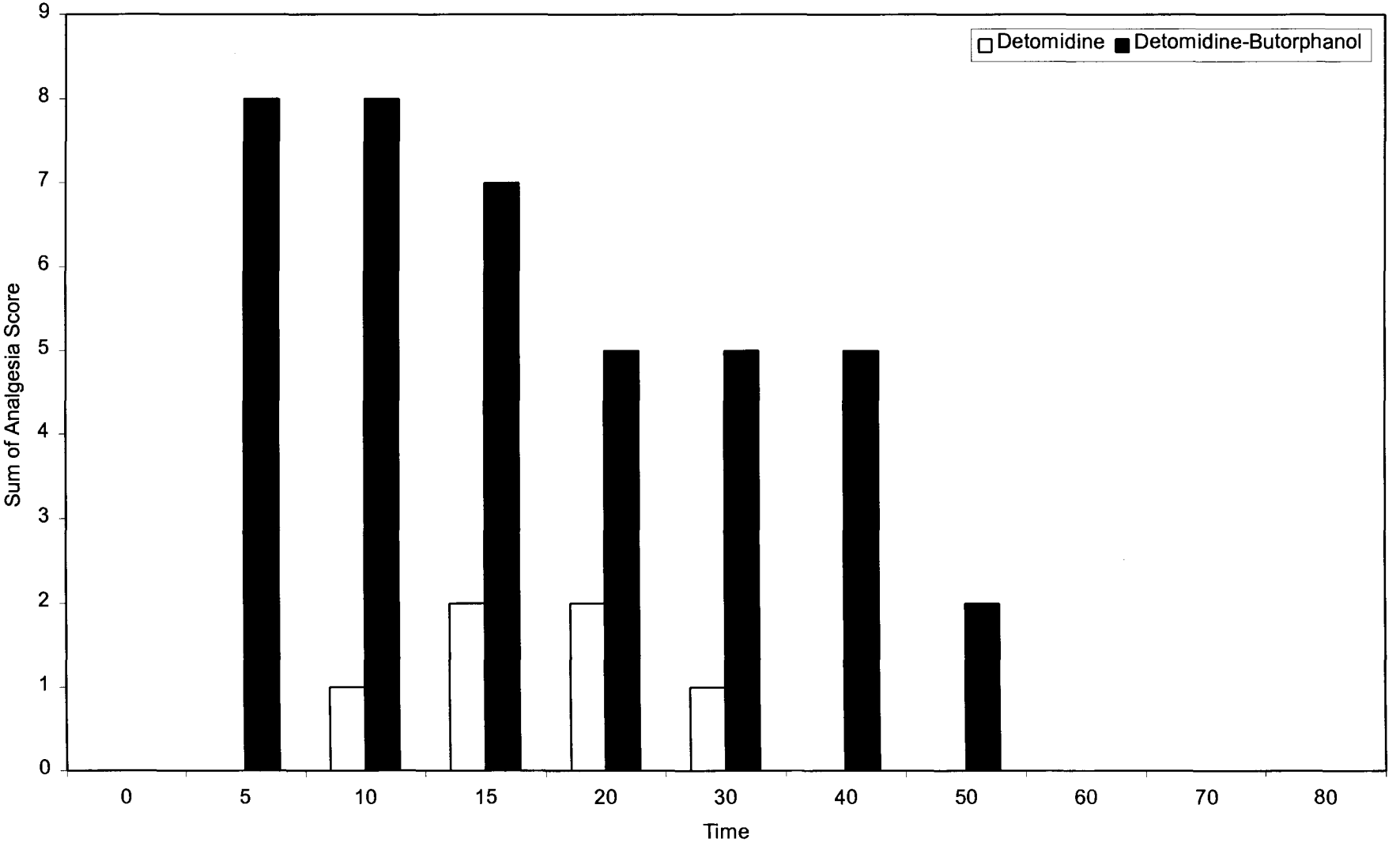


Figure 14: Heart Rate Graph

The mean heart rates for both groups in beats per minute have been plotted against time. Error bars indicate the standard error from mean. The Detomidine group is represented by triangles and the Detomidine-Butorphanol group by dots.

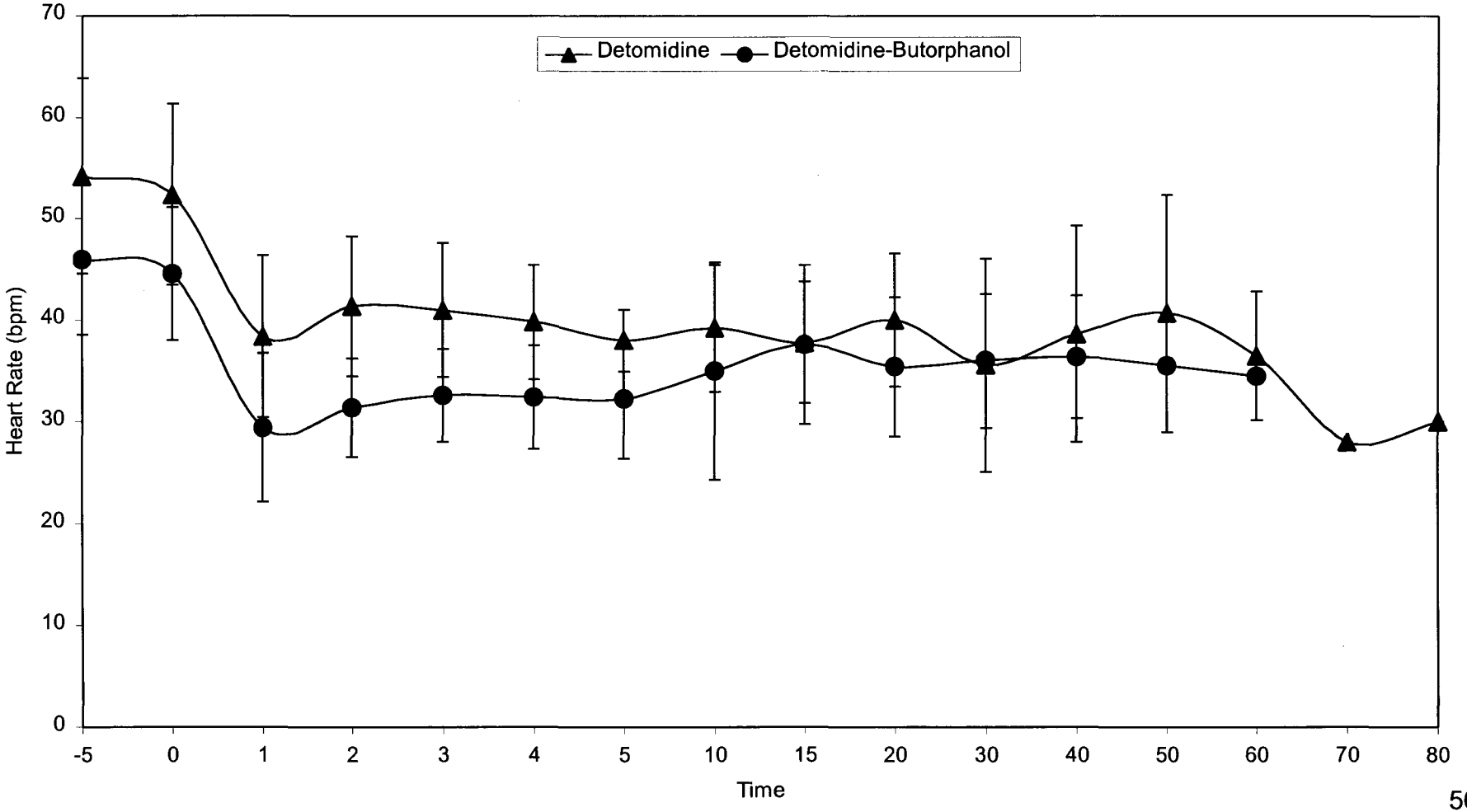
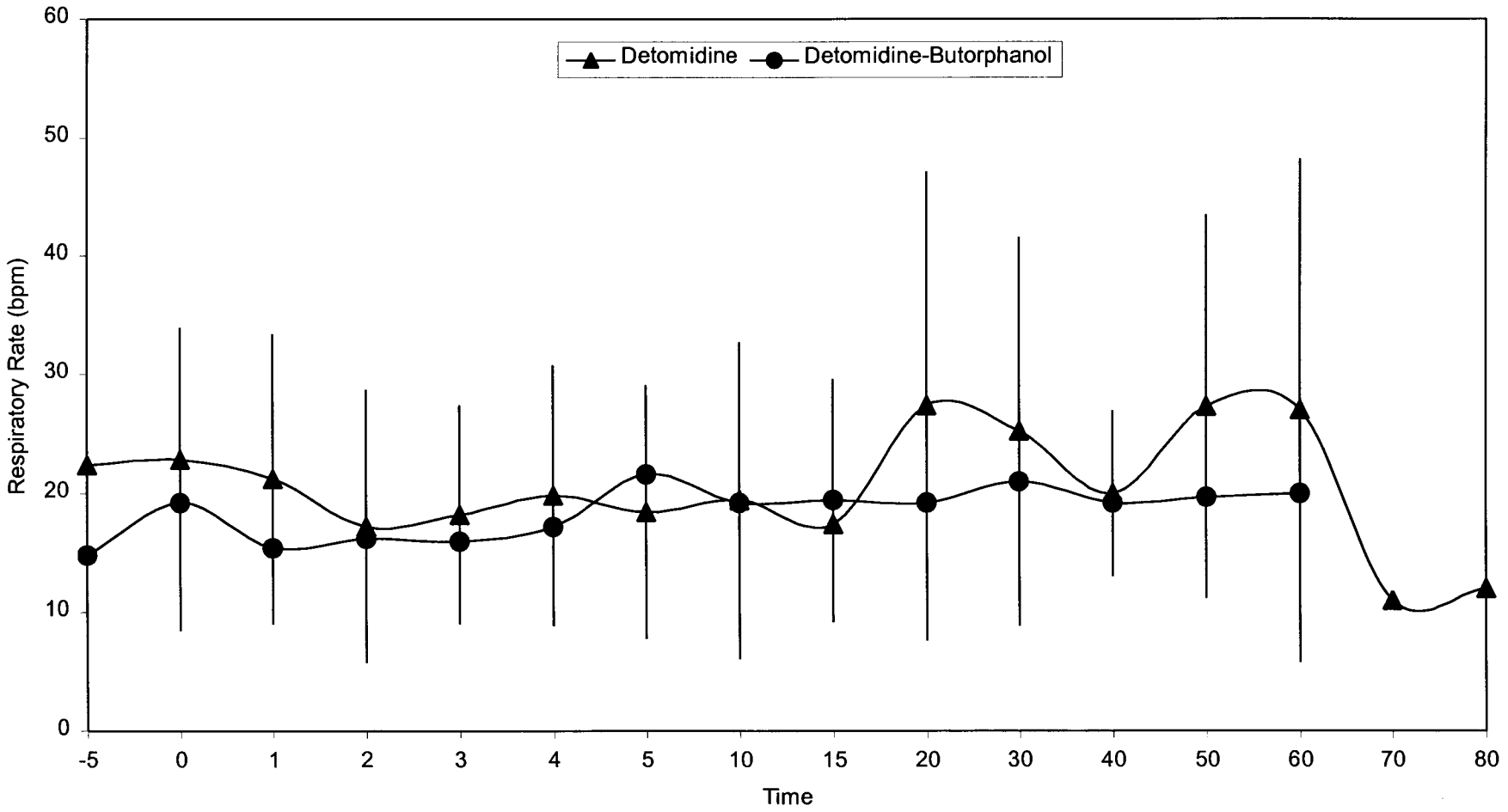


Figure 15: Respiratory Rate Graph

The mean respiratory rates for both groups in breaths per minute have been plotted against time. Error bars indicate the standard error from mean. The Detomidine group is represented by triangles and the Detomidine-Butorphanol group by dots.



Annexe 8: Statistical Analysis of Data

Table 21: Age Analysis

Age	*D*	*DB*
Mean	2.875	6
Variance	1.0625	40.5
Observations	4	4
Hypothesised Mean Difference	0	
Df	3	
t Stat	-0.96946	
P(T<=t) one-tail	0.201912	
t Critical one-tail	2.353363	
P(T<=t) two-tail	0.403825	
t Critical two-tail	3.182449	

Table 22: Body Mass Analysis

Body mass	*D*	*DB*
Mean	138	142
Variance	440	1528
Observations	4	4
Hypothesised Mean Difference	0	
Df	5	
t Stat	-0.18033	
P(T<=t) one-tail	0.431986	
t Critical one-tail	2.015049	
P(T<=t) two-tail	0.863972	
t Critical two-tail	2.570578	

Table 23: Detomidine Dose Analysis

Detomidine Dose	*D*	*DB*
Mean	0.009795	0.0127101
Variance	2.92E-08	2.298E-05
Observations	4	4
Pooled Variance	1.15E-05	
Hypothesized Mean Difference	0	
Df	6	
t Stat	-1.21524	
P(T<=t) one-tail	0.13496	
t Critical one-tail	1.943181	
P(T<=t) two-tail	0.26992	
t Critical two-tail	2.446914	

Table 24: Onset of Sedation Analysis

Onset of sedation	*D*	*DB*
Mean	0.003035	0.002376
Variance	6.15E-08	6.41E-08
Observations	4	4

Hypothesised Mean Difference	0
Df	6
t Stat	3.723886
P(T<=t) one-tail	0.004904
t Critical one-tail	1.943181
P(T<=t) two-tail	0.009807
t Critical two-tail	2.446914

Table 25: Length of Sedation Analysis

Length of Sedation	*D*	*DB*
Mean	0.015231	0.043325
Variance	6E-05	0.000157
Observations	4	4
Hypothesised Mean Difference	0	
Df	5	
t Stat	-3.81199	
P(T<=t) one-tail	0.006237	
t Critical one-tail	2.015049	
P(T<=t) two-tail	0.012475	
t Critical two-tail	2.570578	

Table 26: Length of Procedure Analysis

Length of Procedure	*D*	*DB*
Mean	0.029528	0.030032
Variance	0.000425	5.42E-05
Observations	4	4
Hypothesised Mean Difference	0	
Df	4	
t Stat	-0.04601	
P(T<=t) one-tail	0.482755	
t Critical one-tail	2.131846	
P(T<=t) two-tail	0.965509	
t Critical two-tail	2.776451	

Table 27: Heart Rate Analysis between Points in Time

Detomidine	*0*	*1*
Mean	53.3	38.4
Variance	77.78889	64.3
Observations	10	5
Pooled Variance	73.63846	
Hypothesized Mean Difference	0	
Df	13	
t Stat	3.170102	
P(T<=t) one-tail	0.00369	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.00738	
t Critical two-tail	2.160368	
Detomidine	*0*	*2*
Mean	53.3	41.4

Variance	77.78889	47.3
Observations	10	5
Pooled Variance	68.40769	
Hypothesized Mean Difference	0	
Df	13	
t Stat	2.626841	
P(T<=t) one-tail	0.010456	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.020913	
t Critical two-tail	2.160368	

Detomidine	*0*	*3*
Mean	53.3	41
Variance	77.78889	43.5
Observations	10	5
Pooled Variance	67.23846	
Hypothesized Mean Difference	0	
Df	13	
t Stat	2.738644	
P(T<=t) one-tail	0.00845	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.016901	
t Critical two-tail	2.160368	

Detomidine	*0*	*4*
Mean	53.3	39.8
Variance	77.78889	32.2
Observations	10	5
Pooled Variance	63.76154	
Hypothesized Mean Difference	0	
Df	13	
t Stat	3.086695	
P(T<=t) one-tail	0.004333	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.008666	
t Critical two-tail	2.160368	

Detomidine	*0*	*5*
Mean	53.3	38
Variance	77.78889	9.5
Observations	10	5
Pooled Variance	56.77692	
Hypothesized Mean Difference	0	
Df	13	
t Stat	3.70719	
P(T<=t) one-tail	0.001317	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.002634	
t Critical two-tail	2.160368	

Detomidine	*0*	*10*
Mean	53.3	39.2
Variance	77.78889	39.2
Observations	10	5
Pooled Variance	65.91538	
Hypothesized Mean Difference	0	
Df	13	
t Stat	3.170773	
P(T<=t) one-tail	0.003685	

t Critical one-tail	1.770932	
P(T<=t) two-tail	0.007371	
t Critical two-tail	2.160368	
Detomidine	*0*	*15*
Mean	53.3	37.8
Variance	77.78889	35.7
Observations	10	5
Pooled Variance	64.83846	
Hypothesized Mean Difference	0	
Df	13	
t Stat	3.514429	
P(T<=t) one-tail	0.001904	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.003807	
t Critical two-tail	2.160368	
Detomidine	*0*	*20*
Mean	53.3	40
Variance	77.78889	43
Observations	10	5
Pooled Variance	67.08462	
Hypothesized Mean Difference	0	
Df	13	
t Stat	2.964692	
P(T<=t) one-tail	0.005479	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.010958	
t Critical two-tail	2.160368	
Detomidine	*0*	*30*
Mean	53.3	35.6
Variance	77.78889	110.3
Observations	10	5
Pooled Variance	87.79231	
Hypothesized Mean Difference	0	
Df	13	
t Stat	3.44893	
P(T<=t) one-tail	0.002158	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.004317	
t Critical two-tail	2.160368	
Detomidine	*0*	*40*
Mean	53.3	38.66667
Variance	77.78889	114.3333
Observations	10	3
Pooled Variance	84.43333	
Hypothesized Mean Difference	0	
Df	11	
t Stat	2.419219	
P(T<=t) one-tail	0.017027	
t Critical one-tail	1.795884	
P(T<=t) two-tail	0.034054	
t Critical two-tail	2.200986	
Detomidine	*0*	*50*
Mean	53.3	40.66667
Variance	77.78889	136.3333
Observations	10	3

Pooled Variance	88.43333	
Hypothesized Mean Difference	0	
Df	11	
t Stat	2.040793	
P(T<=t) one-tail	0.033007	
t Critical one-tail	1.795884	
P(T<=t) two-tail	0.066014	
t Critical two-tail	2.200986	
Detomidine	*0*	*60*
Mean	53.3	36.5
Variance	77.78889	40.5
Observations	10	2
Pooled Variance	74.06	
Hypothesized Mean Difference	0	
Df	10	
t Stat	2.520239	
P(T<=t) one-tail	0.015187	
t Critical one-tail	1.812462	
P(T<=t) two-tail	0.030375	
t Critical two-tail	2.228139	
Detomidine	*0*	*70*
Mean	53.3	28
Variance	77.78889	#DIV/0!
Observations	10	1
Pooled Variance	77.78889	
Hypothesized Mean Difference	0	
Df	9	
t Stat	2.735051	
P(T<=t) one-tail	0.011517	
t Critical one-tail	1.833114	
P(T<=t) two-tail	0.023033	
t Critical two-tail	2.262159	
Detomidine	*0*	*80*
Mean	53.3	30
Variance	77.78889	#DIV/0!
Observations	10	1
Pooled Variance	77.78889	
Hypothesized Mean Difference	0	
Df	9	
t Stat	2.518841	
P(T<=t) one-tail	0.016416	
t Critical one-tail	1.833114	
P(T<=t) two-tail	0.032831	
t Critical two-tail	2.262159	
Detomidine-Butorphanol	*0*	*1*
Mean	45.3	29.4
Variance	44.23333	53.3
Observations	10	5
Pooled Variance	47.02308	
Hypothesized Mean Difference	0	
Df	13	
t Stat	4.233319	
P(T<=t) one-tail	0.000489	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.000977	

t Critical two-tail	2.160368	
Detomidine-Butorphanol	*0*	*2*
Mean	45.3	31.4
Variance	44.23333	23.3
Observations	10	5
Pooled Variance	37.79231	
Hypothesized Mean Difference	0	
Df	13	
t Stat	4.128121	
P(T<=t) one-tail	0.000594	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.001189	
t Critical two-tail	2.160368	
Detomidine-Butorphanol	*0*	*3*
Mean	45.3	32.6
Variance	44.23333	20.8
Observations	10	5
Pooled Variance	37.02308	
Hypothesized Mean Difference	0	
Df	13	
t Stat	3.810718	
P(T<=t) one-tail	0.001081	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.002163	
t Critical two-tail	2.160368	
Detomidine-Butorphanol	*0*	*4*
Mean	45.3	32.4
Variance	44.23333	26.3
Observations	10	5
Pooled Variance	38.71538	
Hypothesized Mean Difference	0	
Df	13	
t Stat	3.785187	
P(T<=t) one-tail	0.001135	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.00227	
t Critical two-tail	2.160368	
Detomidine-Butorphanol	*0*	*5*
Mean	45.3	32.2
Variance	44.23333	33.7
Observations	10	5
Pooled Variance	40.99231	
Hypothesized Mean Difference	0	
Df	13	
t Stat	3.735592	
P(T<=t) one-tail	0.001247	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.002495	
t Critical two-tail	2.160368	
Detomidine-Butorphanol	*0*	*10*
Mean	45.3	35
Variance	44.23333	114
Observations	10	5
Pooled Variance	65.7	
Hypothesized Mean Difference	0	

Df	13	
t Stat	2.320032	
P(T<=t) one-tail	0.018624	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.037247	
t Critical two-tail	2.160368	
Detomidine-Butorphanol	*0*	*15*
Mean	45.3	37.6
Variance	44.23333	61.3
Observations	10	5
Pooled Variance	49.48462	
Hypothesized Mean Difference	0	
Df	13	
t Stat	1.998458	
P(T<=t) one-tail	0.033513	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.067025	
t Critical two-tail	2.160368	
Detomidine-Butorphanol	*0*	*20*
Mean	45.3	35.4
Variance	44.23333	47.3
Observations	10	5
Pooled Variance	45.17692	
Hypothesized Mean Difference	0	
Df	13	
t Stat	2.689158	
P(T<=t) one-tail	0.009287	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.018574	
t Critical two-tail	2.160368	
Detomidine-Butorphanol	*0*	*30*
Mean	45.3	36
Variance	44.23333	43.5
Observations	10	5
Pooled Variance	44.00769	
Hypothesized Mean Difference	0	
Df	13	
t Stat	2.559517	
P(T<=t) one-tail	0.01188	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.023761	
t Critical two-tail	2.160368	
Detomidine-Butorphanol	*0*	*40*
Mean	45.3	36.4
Variance	44.23333	36.3
Observations	10	5
Pooled Variance	41.79231	
Hypothesized Mean Difference	0	
Df	13	
t Stat	2.513513	
P(T<=t) one-tail	0.01296	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.025919	
t Critical two-tail	2.160368	
Detomidine-Butorphanol	*0*	*50*

Mean	45.3	35.5
Variance	44.23333	0.5
Observations	10	2
Pooled Variance	39.86	
Hypothesized Mean Difference	0	
Df	10	
t Stat	2.003927	
P(T<=t) one-tail	0.036455	
t Critical one-tail	1.812462	
P(T<=t) two-tail	0.072909	
t Critical two-tail	2.228139	
Detomidine-Butorphanol	*0*	*60*
Mean	45.3	34.5
Variance	44.23333	0.5
Observations	10	2
Pooled Variance	39.86	
Hypothesized Mean Difference	0	
Df	10	
t Stat	2.208409	
P(T<=t) one-tail	0.02585	
t Critical one-tail	1.812462	
P(T<=t) two-tail	0.0517	
t Critical two-tail	2.228139	

Table 28: Heart Rate Analysis between Groups

Time - 5 Minutes	*D*	*DB*
Mean	55	44.5
Variance	119.3333	59
Observations	4	4
Pooled Variance	89.16667	
Hypothesized Mean Difference	0	
Df	6	
t Stat	1.572545	
P(T<=t) one-tail	0.083443	
t Critical one-tail	1.943181	
P(T<=t) two-tail	0.166885	
t Critical two-tail	2.446914	
Time 0 Minutes	*D*	*DB*
Mean	53.5	45.25
Variance	99	54.25
Observations	4	4
Pooled Variance	76.625	
Hypothesized Mean Difference	0	
Df	6	
t Stat	1.332857	
P(T<=t) one-tail	0.115478	
t Critical one-tail	1.943181	
P(T<=t) two-tail	0.230956	
t Critical two-tail	2.446914	
Time 1 Minute	*D*	*DB*
Mean	38.5	30
Variance	85.66667	68.66667
Observations	4	4

Pooled Variance	77.16667
Hypothesized Mean Difference	0
Df	6
t Stat	1.368419
P(T<=t) one-tail	0.110103
t Critical one-tail	1.943181
P(T<=t) two-tail	0.220206
t Critical two-tail	2.446914

Time 2 Minutes	*D*	*DB*
Mean	40.5	32.75
Variance	57.66667	18.91667
Observations	4	4
Pooled Variance	38.29167	
Hypothesized Mean Difference	0	
Df	6	
t Stat	1.771188	
P(T<=t) one-tail	0.063458	
t Critical one-tail	1.943181	
P(T<=t) two-tail	0.126915	
t Critical two-tail	2.446914	

Time 3 Minutes	*D*	*DB*
Mean	39.5	33.75
Variance	43	18.91667
Observations	4	4
Pooled Variance	30.95833	
Hypothesized Mean Difference	0	
Df	6	
t Stat	1.461484	
P(T<=t) one-tail	0.097096	
t Critical one-tail	1.943181	
P(T<=t) two-tail	0.194193	
t Critical two-tail	2.446914	

Time 4 Minutes	*D*	*DB*
Mean	38.25	33.5
Variance	26.91667	27
Observations	4	4
Pooled Variance	26.95833	
Hypothesized Mean Difference	0	
Df	6	
t Stat	1.293785	
P(T<=t) one-tail	0.121654	
t Critical one-tail	1.943181	
P(T<=t) two-tail	0.243309	
t Critical two-tail	2.446914	

Time 5 Minutes	*D*	*DB*
Mean	38	33.5
Variance	12.66667	33.66667
Observations	4	4
Pooled Variance	23.16667	
Hypothesized Mean Difference	0	
Df	6	
t Stat	1.322196	
P(T<=t) one-tail	0.117135	
t Critical one-tail	1.943181	
P(T<=t) two-tail	0.23427	

t Critical two-tail	2.446914	
Time 10 Minutes	*D*	*DB*
Mean	38.75	36.5
Variance	50.91667	137
Observations	4	4
Pooled Variance	93.95833	
Hypothesized Mean Difference	0	
Df	6	
t Stat	0.328269	
P(T<=t) one-tail	0.376931	
t Critical one-tail	1.943181	
P(T<=t) two-tail	0.753862	
t Critical two-tail	2.446914	
Time 15 Minutes	*D*	*DB*
Mean	36.5	39
Variance	36.33333	68.66667
Observations	4	4
Pooled Variance	52.5	
Hypothesized Mean Difference	0	
Df	6	
t Stat	-0.48795	
P(T<=t) one-tail	0.321451	
t Critical one-tail	1.943181	
P(T<=t) two-tail	0.642903	
t Critical two-tail	2.446914	
Time 20 Minutes	*D*	*DB*
Mean	39.25	36.75
Variance	53.58333	50.91667
Observations	4	4
Pooled Variance	52.25	
Hypothesized Mean Difference	0	
Df	6	
t Stat	0.489116	
P(T<=t) one-tail	0.321062	
t Critical one-tail	1.943181	
P(T<=t) two-tail	0.642124	
t Critical two-tail	2.446914	
Time 30 Minutes	*D*	*DB*
Mean	34	37.5
Variance	130	43
Observations	4	4
Pooled Variance	86.5	
Hypothesized Mean Difference	0	
Df	6	
t Stat	-0.5322	
P(T<=t) one-tail	0.306854	
t Critical one-tail	1.943181	
P(T<=t) two-tail	0.613709	
t Critical two-tail	2.446914	
Time 40 Minutes	*D*	*DB*
Mean	37.5	37.25
Variance	220.5	43.58333
Observations	2	4
Pooled Variance	87.8125	
Hypothesized Mean Difference	0	

Df	4
t Stat	0.030806
P(T<=t) one-tail	0.48845
t Critical one-tail	2.131846
P(T<=t) two-tail	0.9769
t Critical two-tail	2.776451

Time 50 Minutes	*D*	*DB*
Mean	39.5	35.5
Variance	264.5	0.5
Observations	2	2
Pooled Variance	132.5	
Hypothesized Mean Difference	0	
Df	2	
t Stat	0.347498	
P(T<=t) one-tail	0.38069	
t Critical one-tail	2.919987	
P(T<=t) two-tail	0.76138	
t Critical two-tail	4.302656	

Time 60 Minutes	*D*	*DB*
Mean	32	34.5
Variance	#DIV/0!	0.5
Observations	1	2
Pooled Variance	0.5	
Hypothesized Mean Difference	0	
Df	1	
t Stat	-2.88675	
P(T<=t) one-tail	0.106148	
t Critical one-tail	6.313749	
P(T<=t) two-tail	0.212296	
t Critical two-tail	12.70615	

D = Detomidine Group, DB = Detomidine – Butorphanol Group

Table 29: Respiratory Rate Analysis between Points in Time

Detomidine	*0*	*1*
Mean	22.6	21.2
Variance	95.82222	148.7
Observations	10	5
Pooled Variance	112.0923	
Hypothesized Mean Difference	0	
Df	13	
t Stat	0.241423	
P(T<=t) one-tail	0.406497	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.812993	
t Critical two-tail	2.160368	

Detomidine	*0*	*2*
Mean	22.6	17.2
Variance	95.82222	131.2
Observations	10	5
Pooled Variance	106.7077	
Hypothesized Mean Difference	0	
Df	13	
t Stat	0.954411	
P(T<=t) one-tail	0.178643	

t Critical one-tail	1.770932	
P(T<=t) two-tail	0.357287	
t Critical two-tail	2.160368	

Detomidine	*0*	*3*
Mean	22.6	18.2
Variance	95.82222	84.2
Observations	10	5
Pooled Variance	92.24615	
Hypothesized Mean Difference	0	
Df	13	
t Stat	0.836407	
P(T<=t) one-tail	0.209018	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.418035	
t Critical two-tail	2.160368	

Detomidine	*0*	*4*
Mean	22.6	19.8
Variance	95.82222	120.2
Observations	10	5
Pooled Variance	103.3231	
Hypothesized Mean Difference	0	
Df	13	
t Stat	0.50292	
P(T<=t) one-tail	0.311716	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.623433	
t Critical two-tail	2.160368	

Detomidine	*0*	*5*
Mean	22.6	18.4
Variance	95.82222	113.3
Observations	10	5
Pooled Variance	101.2	
Hypothesized Mean Difference	0	
Df	13	
t Stat	0.762252	
P(T<=t) one-tail	0.229759	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.459517	
t Critical two-tail	2.160368	

Detomidine	*0*	*10*
Mean	22.6	19.4
Variance	95.82222	177.8
Observations	10	5
Pooled Variance	121.0462	
Hypothesized Mean Difference	0	
Df	13	
t Stat	0.531024	
P(T<=t) one-tail	0.302178	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.604357	
t Critical two-tail	2.160368	

Detomidine	*0*	*15*
Mean	22.6	17.4
Variance	95.82222	54.8
Observations	10	5

Pooled Variance	83.2
Hypothesized Mean Difference	0
Df	13
t Stat	1.040833
P(T<=t) one-tail	0.158462
t Critical one-tail	1.770932
P(T<=t) two-tail	0.316924
t Critical two-tail	2.160368

Detomidine	*0*	*20*
Mean	22.6	27.4
Variance	95.82222	389.8
Observations	10	5
Pooled Variance	186.2769	
Hypothesized Mean Difference	0	
Df	13	
t Stat	-0.6421	
P(T<=t) one-tail	0.265985	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.53197	
t Critical two-tail	2.160368	

Detomidine	*0*	*30*
Mean	22.6	25.2
Variance	95.82222	267.2
Observations	10	5
Pooled Variance	148.5538	
Hypothesized Mean Difference	0	
Df	13	
t Stat	-0.38947	
P(T<=t) one-tail	0.351618	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.703236	
t Critical two-tail	2.160368	

Detomidine	*0*	*40*
Mean	22.6	20
Variance	95.82222	48
Observations	10	3
Pooled Variance	87.12727	
Hypothesized Mean Difference	0	
Df	11	
t Stat	0.423141	
P(T<=t) one-tail	0.340173	
t Critical one-tail	1.795884	
P(T<=t) two-tail	0.680347	
t Critical two-tail	2.200986	

Detomidine	*0*	*50*
Mean	22.6	27.33333
Variance	95.82222	261.3333
Observations	10	3
Pooled Variance	125.9152	
Hypothesized Mean Difference	0	
Df	11	
t Stat	-0.64079	
P(T<=t) one-tail	0.26739	
t Critical one-tail	1.795884	
P(T<=t) two-tail	0.53478	

t Critical two-tail	2.200986	
Detomidine	*0*	*60*
Mean	22.6	27
Variance	95.82222	450
Observations	10	2
Pooled Variance	131.24	
Hypothesized Mean Difference	0	
Df	10	
t Stat	-0.49584	
P(T<=t) one-tail	0.315361	
t Critical one-tail	1.812462	
P(T<=t) two-tail	0.630721	
t Critical two-tail	2.228139	
Detomidine	*0*	*70*
Mean	22.6	11
Variance	95.82222	#DIV/0!
Observations	10	1
Pooled Variance	95.82222	
Hypothesized Mean Difference	0	
Df	9	
t Stat	1.12987	
P(T<=t) one-tail	0.143872	
t Critical one-tail	1.833114	
P(T<=t) two-tail	0.287743	
t Critical two-tail	2.262159	
Detomidine	*0*	*80*
Mean	22.6	12
Variance	95.82222	#DIV/0!
Observations	10	1
Pooled Variance	95.82222	
Hypothesized Mean Difference	0	
Df	9	
t Stat	1.032468	
P(T<=t) one-tail	0.164399	
t Critical one-tail	1.833114	
P(T<=t) two-tail	0.328799	
t Critical two-tail	2.262159	
Detomidine-Butorphanol	*0*	*1*
Mean	17	15.4
Variance	60.88889	12.8
Observations	10	5
Pooled Variance	46.09231	
Hypothesized Mean Difference	0	
Df	13	
t Stat	0.430274	
P(T<=t) one-tail	0.337022	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.674043	
t Critical two-tail	2.160368	
Detomidine-Butorphanol	*0*	*2*
Mean	17	16.2
Variance	60.88889	27.2
Observations	10	5
Pooled Variance	50.52308	
Hypothesized Mean Difference	0	

Df	13
t Stat	0.205487
P(T<=t) one-tail	0.420187
t Critical one-tail	1.770932
P(T<=t) two-tail	0.840374
t Critical two-tail	2.160368

Detomidine-Butorphanol	*0*	*3*
Mean	17	16
Variance	60.88889	18.5
Observations	10	5
Pooled Variance	47.84615	
Hypothesized Mean Difference	0	
Df	13	
t Stat	0.263946	
P(T<=t) one-tail	0.39798	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.795959	
t Critical two-tail	2.160368	

Detomidine-Butorphanol	*0*	*4*
Mean	17	17.2
Variance	60.88889	31.7
Observations	10	5
Pooled Variance	51.90769	
Hypothesized Mean Difference	0	
Df	13	
t Stat	-0.05068	
P(T<=t) one-tail	0.480175	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.960349	
t Critical two-tail	2.160368	

Detomidine-Butorphanol	*0*	*5*
Mean	17	21.6
Variance	60.88889	54.3
Observations	10	5
Pooled Variance	58.86154	
Hypothesized Mean Difference	0	
Df	13	
t Stat	-1.09467	
P(T<=t) one-tail	0.146765	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.293531	
t Critical two-tail	2.160368	

Detomidine-Butorphanol	*0*	*10*
Mean	17	19.2
Variance	60.88889	57.2
Observations	10	5
Pooled Variance	59.75385	
Hypothesized Mean Difference	0	
Df	13	
t Stat	-0.51961	
P(T<=t) one-tail	0.306034	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.612067	
t Critical two-tail	2.160368	

Detomidine-Butorphanol	*0*	*15*

Mean	17	19.4
Variance	60.88889	104.8
Observations	10	5
Pooled Variance	74.4	
Hypothesized Mean Difference	0	
Df	13	
t Stat	-0.508	
P(T<=t) one-tail	0.309981	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.619963	
t Critical two-tail	2.160368	

Detomidine-Butorphanol	*0*	*20*
Mean	17	19.2
Variance	60.88889	51.2
Observations	10	5
Pooled Variance	57.90769	
Hypothesized Mean Difference	0	
Df	13	
t Stat	-0.52783	
P(T<=t) one-tail	0.303255	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.60651	
t Critical two-tail	2.160368	

Detomidine-Butorphanol	*0*	*30*
Mean	17	21
Variance	60.88889	80
Observations	10	5
Pooled Variance	66.76923	
Hypothesized Mean Difference	0	
Df	13	
t Stat	-0.89374	
P(T<=t) one-tail	0.193854	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.387708	
t Critical two-tail	2.160368	

Detomidine-Butorphanol	*0*	*40*
Mean	17	19.2
Variance	60.88889	23.7
Observations	10	5
Pooled Variance	49.44615	
Hypothesized Mean Difference	0	
Df	13	
t Stat	-0.57121	
P(T<=t) one-tail	0.2888	
t Critical one-tail	1.770932	
P(T<=t) two-tail	0.577599	
t Critical two-tail	2.160368	

Detomidine-Butorphanol	*0*	*50*
Mean	17	19.66667
Variance	60.88889	44.33333
Observations	10	3
Pooled Variance	57.87879	
Hypothesized Mean Difference	0	
Df	11	
t Stat	-0.53247	

P(T<=t) one-tail	0.302494	
t Critical one-tail	1.795884	
P(T<=t) two-tail	0.604987	
t Critical two-tail	2.200986	
Detomidine-Butorphanol	*0*	*60*
Mean	17	20
Variance	60.88889	#DIV/0!
Observations	10	1
Pooled Variance	60.88889	
Hypothesized Mean Difference	0	
Df	9	
t Stat	-0.36657	
P(T<=t) one-tail	0.361205	
t Critical one-tail	1.833114	
P(T<=t) two-tail	0.72241	
t Critical two-tail	2.262159	

Table 30: Respiratory Rate Analysis between Groups

Time -5	*D*	*DB*
Mean	22.4	14.8
Variance	90.8	9.7
Observations	5	5
Pooled Variance	50.25	
Hypothesized Mean Difference	0	
Df	8	
t Stat	1.695179	
P(T<=t) one-tail	0.064243	
t Critical one-tail	1.859548	
P(T<=t) two-tail	0.128487	
t Critical two-tail	2.306006	
Time 0	*D*	*DB*
Mean	22.8	19.2
Variance	124.7	115.2
Observations	5	5
Pooled Variance	119.95	
Hypothesized Mean Difference	0	
Df	8	
t Stat	0.519724	
P(T<=t) one-tail	0.308663	
t Critical one-tail	1.859548	
P(T<=t) two-tail	0.617327	
t Critical two-tail	2.306006	
Time 1	*D*	*DB*
Mean	21.2	15.4
Variance	148.7	12.8
Observations	5	5
Pooled Variance	80.75	
Hypothesized Mean Difference	0	
Df	8	
t Stat	1.020532	
P(T<=t) one-tail	0.168671	
t Critical one-tail	1.859548	
P(T<=t) two-tail	0.337343	

t Critical two-tail	2.306006	
Time 2	*D*	*DB*
Mean	17.2	16.2
Variance	131.2	27.2
Observations	5	5
Pooled Variance	79.2	
Hypothesized Mean Difference	0	
Df	8	
t Stat	0.177667	
P(T<=t) one-tail	0.4317	
t Critical one-tail	1.859548	
P(T<=t) two-tail	0.8634	
t Critical two-tail	2.306006	
Time 3	*D*	*DB*
Mean	18.2	16
Variance	84.2	18.5
Observations	5	5
Pooled Variance	51.35	
Hypothesized Mean Difference	0	
Df	8	
t Stat	0.485425	
P(T<=t) one-tail	0.320195	
t Critical one-tail	1.859548	
P(T<=t) two-tail	0.640389	
t Critical two-tail	2.306006	
Time 4	*D*	*DB*
Mean	19.8	17.2
Variance	120.2	31.7
Observations	5	5
Pooled Variance	75.95	
Hypothesized Mean Difference	0	
Df	8	
t Stat	0.471715	
P(T<=t) one-tail	0.324864	
t Critical one-tail	1.859548	
P(T<=t) two-tail	0.649728	
t Critical two-tail	2.306006	
Time 5	*D*	*DB*
Mean	18.4	24
Variance	113.3	34
Observations	5	4
Pooled Variance	79.31429	
Hypothesized Mean Difference	0	
Df	7	
t Stat	-0.93736	
P(T<=t) one-tail	0.18989	
t Critical one-tail	1.894578	
P(T<=t) two-tail	0.379779	
t Critical two-tail	2.364623	
Time 10	*D*	*DB*
Mean	19.4	19.2
Variance	177.8	57.2
Observations	5	5
Pooled Variance	117.5	
Hypothesized Mean Difference	0	

Df	8
t Stat	0.029173
P(T<=t) one-tail	0.488721
t Critical one-tail	1.859548
P(T<=t) two-tail	0.977441
t Critical two-tail	2.306006

Time 15	*D*	*DB*
Mean	17.4	19.4
Variance	54.8	104.8
Observations	5	5
Pooled Variance	79.8	
Hypothesized Mean Difference	0	
Df	8	
t Stat	-0.354	
P(T<=t) one-tail	0.366245	
t Critical one-tail	1.859548	
P(T<=t) two-tail	0.732491	
t Critical two-tail	2.306006	

Time 20	*D*	*DB*
Mean	27.4	19.2
Variance	389.8	51.2
Observations	5	5
Pooled Variance	220.5	
Hypothesized Mean Difference	0	
Df	8	
t Stat	0.873131	
P(T<=t) one-tail	0.204017	
t Critical one-tail	1.859548	
P(T<=t) two-tail	0.408034	
t Critical two-tail	2.306006	

Time 30	*D*	*DB*
Mean	25.2	21
Variance	267.2	80
Observations	5	5
Pooled Variance	173.6	
Hypothesized Mean Difference	0	
Df	8	
t Stat	0.504016	
P(T<=t) one-tail	0.313917	
t Critical one-tail	1.859548	
P(T<=t) two-tail	0.627835	
t Critical two-tail	2.306006	

Time 40	*D*	*DB*
Mean	20	19.2
Variance	48	23.7
Observations	3	5
Pooled Variance	31.8	
Hypothesized Mean Difference	0	
Df	6	
t Stat	0.194257	
P(T<=t) one-tail	0.426192	
t Critical one-tail	1.943181	
P(T<=t) two-tail	0.852385	
t Critical two-tail	2.446914	

Time 50	*D*	*DB*

Mean	27.33333	19.66667
Variance	261.3333	44.33333
Observations	3	3
Pooled Variance	152.8333	
Hypothesized Mean Difference	0	
Df	4	
t Stat	0.759527	
P(T<=t) one-tail	0.244919	
t Critical one-tail	2.131846	
P(T<=t) two-tail	0.489837	
t Critical two-tail	2.776451	

Time 60	*D*	*DB*
Mean	27	20
Variance	450	#DIV/0!
Observations	2	1
Pooled Variance	450	
Hypothesized Mean Difference	0	
Df	1	
t Stat	0.26943	
P(T<=t) one-tail	0.416227	
t Critical one-tail	6.313749	
P(T<=t) two-tail	0.832454	
t Critical two-tail	12.70615	

Chapter 8

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