The influence of pre-operative antibiotic administration on post-operative morbidity in dental implant placement

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Declaration

I declare that this thesis has not been submitted as an exercise for a degree at any other university. It consists of my own work, except where due acknowledgement has been made in the text.

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Rory Nolan

September 2009

Summary

The success of dental implants for the rehabilitation of both the partially and fully edentulous patient is well documented in the scientific literature. There are no clear guidelines on the use of prophylactic antibiotics in dental implant surgery. There are different protocols being used worldwide and these are often adopted at the surgeons' discretion. There are obvious risks associated with the over prescription of antibiotics such as adverse effects and the increasing emergence of resistant bacterial strains.

A prospective double blind randomised controlled trial was conducted to test the influence of prophylactic antibiotics on post-operative morbidity and osseointegration of dental implants.

The study sample consisted of 55 patients who complied with the admission criteria. 3g Amoxicillin was given pre-operatively as the test (N=27), and compared to a placebo drug given pre-operatively as the control (N=28). No post-operative antibiotics were prescribed. Pain diaries and interference with daily activities diaries were kept by the patient for one week using visual analogue scale questionnaires. Signs of post-operative morbidity (swelling, bruising, suppuration, and wound dehiscence) were recorded by the author after 2 and 7 days. Osseointegration was assessed 3 to 4 months post-operatively or at 2nd stage surgery.

The results of this study suggest that the use of prophylactic pre-operative antibiotics may result in higher dental implant survival rates (100% versus

82%). Five implant failures, 1 in each of 5 patients were reported in the placebo group and none in the antibiotic group ($p=0.05$).

No statistically significant differences were found for any of the signs of post-operative morbidity (swelling, bruising, suppuration and wound dehiscence) at either 2 or 7 days, except for bruising after 2 days, which appeared to be significantly higher in the placebo group ($p=0.05$).

Post-operative pain ($p=0.01$) and interference with daily activity ($p=0.01$) appeared to be significantly lower for the antibiotic group after 7 days.

Those patients with implant failure reported higher pain (VAS scores) after 2 days ($p=0.003$) and after 7 days ($p=0.0005$). Those patients with implant failure also reported higher pain (number of analgesics used) after 7 days ($p=0.001$). Those patients with implant failure also reported higher interference with daily activities (VAS scores) after 2 days ($p=0.005$).

Longer duration of surgery showed a significant but modest correlation with post-operative pain (VAS scores) after 2 days ($r=0.3$). Longer duration of surgery also showed a significant but modest correlation with post-operative pain (number of analgesics used) after 7 days ($r=0.4$). Longer duration of surgery also showed significant but modest correlations with interference with daily activities after 2 days ($r=0.3$) and after 7 days ($r=0.4$).

Longer incision length showed significant but modest correlations with interference with pain (VAS scores) after 2 days ($r=0.3$) and after 7 days

(r=0.3). Longer incision length also showed a significant but modest correlation with interference with pain (number of analgesics used) after 7 days (r=0.4). Longer incision length also showed significant but modest correlations with interference with daily activities (VAS scores) after 2 days (r=03) and after 7 days (r=0.3).

The use of prophylactic antibiotics for dental implant surgery may be justified, as they appear to improve implant survival and also seem to result in less post-operative pain and interference with daily activities.

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1.   Introduction

1.1 *Osseointegration*

The earliest known dental implant dates as far back as 100 A.D., the implant made of wrought iron was found in a skull in a french cemetery. It is thought that the original tooth was used as a mould and the implant was implanted shortly after extraction of the tooth (Crubzy et al. 1998).

The major breakthrough in modern implantology came in 1952 and was the result of experiments being carried out by a Swedish orthopaedic surgeon, Professor Per-Ingvar Brånemark. Following studies using titanium chambers to analyse the blood flow in the tibia of rabbits, he found bone growing directly onto the titanium surface and an inability to remove them from the tibia. This discovery resulted in the principle of osseointegration, which was subsequently defined as "a direct structural and functional connection between ordered living bone and the surface of a load carrying implant" (Brånemark 1985).

It wasn't until 1965 that Professor Brånemark placed the first titanium dental implant into a human volunteer. Since then, long-term clinical studies have provided the scientific evidence for osseointegration with titanium implants (Adell et al. 1981).

Some dental implant failures may be due to bacterial contamination at implant insertion. Infections around biomaterials are difficult to treat and almost all infected implants have to be removed (Esposito et al. 2003).

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1.2 Antibiotic Prophylaxis Regimens

Different types of surgery result in different rates of post-operative infection. Oral surgical procedures including surgical implant placement are considered clean contaminated surgery, as the operation enters a non-infected area but may encounter bacteria and as such have an expected infection rate of less than 7.5%.

Different anti-microbial prophylaxis protocols have been employed for the surgical placement of dental implants. The three main variables in each of these protocols have been:

1. Choice of drug.

2. Dose of drug.

3. Time-point of administration.

It is clear that the anti-microbial chosen should be effective against the bacteria causing any infection. These bacteria include aerobic streptococci, anaerobic gram-positive cocci and anaerobic gram-negative rods. Also the anti-microbial should be bactericidal and non-toxic. Taking these guidelines into consideration, penicillin is the first choice anti-microbial for prophylaxis in dental implant surgery (Peterson 1990; Page et al. 1993).

Periodontists and oral surgeons often prescribe prophylactic antibiotics routinely following gingivectomy (Stahl et al. 1969), osseous resective surgery (Kidd & Wade 1974), regenerative surgery (Cortellini & Bowers 1995) and implant related surgery (Dent et al. 1997). However, some reports have shown that antibiotics provide no advantage in preventing post-operative infections or

affecting the outcomes of periodontal surgery including gingivectomy (Pack & Haber 1983), mucogingival surgery (Checchi et al. 1992), osseous grafts (Pack & Haber 1983) and also the surgical placement of dental implants (Gynther et al. 1998).

The use of prophylactic antibiotics in dental implant surgery remains controversial with different studies reporting conflicting data on their efficacy.

1.3 Pain and Anxiety

Oral surgery is a common procedure that is rarely life threatening, however its' physical and psychological effects mean it still remains a stressful experience and a barrier to seeking dental care (Eli et al. 2003). While there are many studies on pain associated with the surgical removal of teeth, very little data exists on pain experience following placement of dental implants. Hashem et al. describes the pain following dental implant placement to be mild to moderate in nature (Hashem et al. 2006).

It is well documented that when anxiety exists, one is more perceptive of the pain from noxious events such as dental implant placement (Weisenberg 1977, von Graffenried et al. 1978). Oral surgery is both a stressful and anxiety producing procedure in dentistry and management of a patients' anxiety is central to patients' pain control (Eli et al. 1997).

1.4 Principal research question

Does the use of pre-operative prophylactic antibiotics have a positive effect on the post-operative morbidity and pain associated with dental implant surgery, and does it result in improved rates of successful osseointegration of dental implants?

A prospective, double blind, placebo-controlled, randomised clinical trial will be carried out in order to try to answer the above question.

1.4.1 Clinical Relevance

Over one million dental implants are placed worldwide every year. Various antibiotic prophylaxis regimens are used which may not be necessary. This may add to the increasing emergence of resistant bacterial strains, produce unwanted adverse effects in patients, and cause unneeded economic waste.

To date there are no clear guidelines on the correct antibiotic prophylaxis regimen to be used in dental implant surgery.

1.5   Aims and Objectives

The aims of this study were as follows:

1. To investigate the influence of pre-operative prophylactic antibiotics on post-operative morbidity (swelling, bruising, wound dehiscence and suppuration) in dental implant surgery.

2. To investigate the influence of pre-operative prophylactic antibiotics on post-operative pain and interference with daily activities.

3. To investigate the influence of pre-operative prophylactic antibiotics on the successful osseointegration of dental implants.

This study will follow on from two previous studies carried out in the School of Dental Science, Trinity College Dublin.

Firstly, Dr. Atef Hashem wrote his thesis on the pain experience following dental implant placement.

Secondly, Dr. Maher Kemmoona wrote his thesis on the influence of pre-operative prophylactic antibiotics on post-operative morbidity in dental implant surgery. The design of the present study is identical to that of Dr. Kemmoona, and I am therefore collating my results with his.

2. Literature Review

2.1 Infection Rates in Surgery

Different types of surgery result in different rates of post-operative infection. It is clearly evident that major open surgery including implanting large foreign materials and surgery involving infected sites are much more likely to cause post-operative infection than minor superficial or even keyhole surgery. Different surgical disciplines have all published varying infection rates for the range of procedures carried out. A wound classification system can be used to predict the incidence of post-operative infection following various types of surgery, Table 2.1.

	Surgery Classification	Infection Rate
1.	Clean wounds	~ 1.5%
2.	Clean contaminated wounds	~ 7.5%
3.	Contaminated wounds	~ 15%
4	Dirty wounds	~ 40%

Table 2.1 Wound classification system and corresponding infection rates.

These classifications are important in the decision making process behind reducing infection rates while keeping procedures practical and safe for the patient. Oral surgical procedures including surgical implant placement are considered clean contaminated surgery, as the operation enters a non-infected area but may encounter bacteria.

2.2 Antiseptics in Surgery

Clinical disinfection first appeared late in the nineteenth century when an Austrian-Hungarian physician, Ignaz Semmelweiss, discovered that the incidence of puerperal fever could be drastically cut by the introduction of hand washing with chlorinated lime solution in obstetric clinics (Semmelweiss 1861).

The use of antiseptics in surgery can be attributed to Joseph Lister, who in 1867 published a report called "Antiseptic Principle Of The Practice Of Surgery". He successfully introduced carbolic acid or phenol, to both clean wounds and to sterilize instruments. This was a new approach to treatment and its' beneficial results rank it as one of the great discoveries of its' time, indeed some consider Lister to be "the father of modern antiseptics"

The introduction of the surgical glove can be attributed to one of the USA's finest surgeons, William Halsted in 1889. He hired the Goodyear Rubber Company to manufacture thin gloves with the necessary sensitivity after the head operating nurse developed dermatitis from the chemicals used to disinfect hands for surgery. Halsted didn't realise at the time the impact of gloves on antisepsis and later went on to create surgical gowns and hats.

Today it is standard procedure to use alcohol, bisguanides and iodides, either singly or in combination both pre- and post-operatively. Their effective and simple application makes them a useful tool in preventing and even treating peri-operative infections.

2.3   Antibiotics in Surgery

Penicillin was first discovered as an antibacterial substance by Sir Alexander Fleming in 1928 (Grandin 1945). An accidental discovery, while researching the properties of *staphylococci* he found a culture contaminated with a fungus and that the colonies of *staphylococci* neighbouring had been destroyed. Fleming later identified the mould as being from the Penicillum genus and months later on the 7th March 1929 named the substance penicillin (Diggins 2003). It wasn't until the 1940's, with the help of Ernst Chain and Howard Florey that penicillin was finally mass produced. The discovery was ranked as the most important discovery of the millennium with an estimated two hundred million lives having been saved by it.

The prophylactic use of penicillin is only indicated for patients at risk of bacterial endocarditis, for patients with a reduced immune response, when surgery is performed in infected sites, in cases of extensive or prolonged surgical interventions and when large foreign materials are implanted. Antibiotic prophylaxis can also be indicated for surgery when either the risk of infection is high, as in clean-contaminated, contaminated and dirty surgery, or when the sequelae to that infection are potentially grave and serious, such as in a total hip replacement in an elderly lady with a reduced immune response.

2.4 Antimicrobial Resistance

The emergence of bacterial resistance to commonly used antibiotics is a growing problem in medicine and dentistry (Ashley et al. 1960; Standing Medical Avisory Committee Sub-Group on Antimcrobial Resistance 1998). Antimicrobial resistance has now been classified as a national security risk in the USA (Kaldec et al. 1997; The global infectious disease threat and its implications for the USA 1999) and is the cause of professional, governmental and public concern (Neu 1992; Tomasz 1994). Whilst this is a growing problem, its' growth is accelerated by the use and misuse of antimicrobials (WHO Global Strategy 2001). Literature reporting antibiotic resistance varies widely both geographically and with regard to specific micro-organisms.

Over prescription, poor compliance and bacterial mutagenic potential have all been blamed for this, including the over-the-counter availability of these drugs without professional control (Smith et al. 1996) and the use of antimicrobials of low potency and effectiveness (Taylor et al. 1995; McGregor A. 1997). Antimicrobial resistance is a global problem and we are all responsible for the containment of this problem.

Encouraging more appropriate and rational use of antimicrobials are key long-term interventions for the containment of antimicrobial resistance (Smith et al. 1996; WHO Global Strategy 2001). It follows that we need to have clear guidelines on the prophylactic prescription of antimicrobials in implant dentistry.

Perhaps the problem is more to do with our general poor understanding of their desired mode of action, their properties and their limitations. It is difficult to obtain data on antibiotic use in most European countries. One article reported a four fold difference in sales of antibiotics among some European Union counties and also a marked difference on the use of various types of antimicrobials (Cars et al. 2001). It is reasonable to expect similar trends in the prescription of antimicrobials, literature reporting large variation may imply poor professional knowledge on the subject.

It could be argued that the conscientious practitioner must cover all avenues of care in an attempt to both cure and prevent infections. However, perhaps the practitioner would be doing more service to their patients were he or she to withhold those antibiotics unless absolutely necessary. Lastly with regards to the overuse of antibiotics, it is the drug companies themselves, or even microbiological testing companies that are pushing for more business that they advocate and even encourage the use of antibiotics for the treatment of conditions that have alternative, safer and sometimes more effective treatment options.

Literature reporting antibiotic resistance varies widely both geographically and with regard to specific micro-organisms.

2.5   Adverse reactions to Antibiotics

Various adverse events have been reported following the use of antibiotics. These can include low grade gastrointestinal upset, colonization of resistant or

fungal strains, cross reaction with other drugs and a type IV hypersensitivity reaction which may result in fatality (Lawler et al. 2005).

Mild reactions including uticaria occur in 0.7-10 per cent of penicillin courses, with a usual range of 1-3% (Idsoe et al. 1968). For every one million patients receiving oral amoxicillin, mild, moderate and severe side-effects will result in 2,400, 400 and 0.9 patients respectively (Clemens & Ransohoff 1984). It has been reported that this rate has and will increase over time as exposure increases (Lawler et al. 2005). Anaphylactic reactions occur in 0.04-0.011% of patients receiving penicillin for prophylaxis and of these cases 10% are fatal (Parker 1982).

2.6   *Dental Implants*

2.6.1   History of Dental Implants

The earliest known dental implants date as far back as 100 A.D., the implant made of wrought iron was found in a skull in a French cemetery. It is thought that the original tooth was used as a mould and the implant was implanted shortly after extraction of the tooth (Crubzy et al. 1998).

A fourteen hundred year old mandible dating as far back as 600 A.D., found while excavating Mayan burial sites in Honduras showed evidence that they had used pieces of shell to fabricate crude dental implants. Compact bone

formation surrounding the shell indicated that the implants had been placed whilst the subject was alive.

Throughout the 20th century dentists were utilising various mechanical and surgical concepts to use implants in the rehabilitation of edentulous mouths. These included the subperiosteal implant which was surgically placed beneath the periosteum and was subsequently encapsulated by a fibrous capsule, and the blade implant which was placed intraosseossly but with the usual result of fibrointegration. Their limited success resulted in poor acceptance by the dental profession.

2.6.2   Modern Implantology

The major breakthrough in modern implantology came in 1952 and was the result of experiments being carried out by a Swedish orthopaedic surgeon, Professor Per-Ingvar Brånemark.

Following on from the study model used in Cambridge in the 1950s, titanium chambers were used in order to study blood flow in the tibias of rabbits. The discovery came when the research team were unable to remove the expensive chambers from the bone, Professor Brånemark observed that bone had adhered to the titanium metal. This new discovery led to the principle of osseointegration, which was subsequently defined as "a direct structural and functional connection between ordered living bone and the surface of a load carrying implant" (Brånemark 1985).

It wasn't until 1965 that Professor Brånemark placed the first titanium dental implant into a human volunteer. Since then, long term clinical studies have provided the scientific evidence for osseointegration using titanium (Adell et al. 1981).

2.6.3 Osseointegration

Osseointegration was defined by Zarb and Albrektsson in 1991 as "a process whereby clinically asymptomatic rigid fixation of alloplastic materials is achieved and maintained during functional loading".

Criteria for implant success were put forward by Albrektsson et al. (1986):

1. That an individual unattached implant is immobile when tested clinically.

2. That a radiograph does not demonstrate any evidence of peri-implant radiolucency.

3. That vertical bone loss be no more than 0.2mm annually following the first year of service.

4. That an individual implant performance be characterized by an absence of persistent and/or irreversible signs and symptoms such as, pain, infection, neuropathy, paraesthesia and violation of the mandibular canal.

5. That in the context of the above, a successful rate of 85% at the end of a 5 year period and 80% at the end of a 10 year period be a minimum criteria for success.

Survival rates of dental implants have now surpassed this early criteria laid down by Albrektsson et al. 1986, mainly due to improvements in micro- and macro-characteristics of implants such as surface topography and in surgical and restorative protocols.

2.6.4   Dental Implant Survival

The use of dental implants for the rehabilitation of partially and fully edentulous mouths is well documented in the scientific literature. In one of the earliest reports on single tooth implants, Schmitt and Zarb (1993) observed that after an average of 3 years, 100% of the implants had survived. Lindh et al. (1998) also showed in a meta-analyses that after 6-7 years a survival rate of 97.5% could be expected from single tooth implants. In a systematic review by Creugers et al. (2000), a 97% implant survival rate was observed after 4 years. Goodacre et al. (2003) tried to accumulate data from various studies to form a general trend from the heterogeneous data present in the literature. He reported a mean implant loss of 3% from combining a number of studies that followed implant survival from 1 to 10 years.

While long-term implant success rates of 97% and above are now routinely expected under optimal conditions, successful osseointegration is far from guaranteed in a number of clinical situations (Fiorellini et al. 1998).

Factors affecting the survival of dental implants can be: 1. Implant related (material, length, width, surface, and design); 2. Surgery related (aseptic technique, use of prophylactic antibiotics, operator experience, initial stability,

immediate, one stage or two stage, and use of simultaneous bone graft); 3. Patient related (presence of systemic disease, smoking status, history of periodontal disease, irradiation therapy, taking bisphosphonate medication, and the quality and quantity of the available bone); and 4. Post-surgery related (loading protocols and the risk of peri-implant disease). Risk factors for failure include a history of smoking, irradiation therapy and impaired bone vascularity (Goodacre et al. 2003). In particular, increased failure rates have been reported in areas with low bone density or reduced bone height in the posterior maxilla. This has been especially the case for screw type implants with a machined surface (Jaffin & Berman 1991; Jemt, 1993).

Surface topography or roughness can have in impact on the rate of osseointegration of the implant with the surrounding bone. Wennerberg et al. (1996) using histomorphometric analysis, observed higher bone to metal contact for grit blasted implants which were removed 12 weeks after placement in rabbit femurs. Wennerberg et al. (1997) again compared the difference in percentage of bone-to-metal contact, and removal torque for three different implant surface, a machined or smooth surface, and two surfaces blasted with different resultant degrees of surface roughness. After one year in the rabbit bone, firmer bone fixation was observed for the two blasted surfaces, with significant differences in removal torque, and percentage of bone-to-metal contact. Klokkevold et al. (2001) compared torque removal forces for machined, dual acid-etched and titanium plasma sprayed implants. Again both rough surface implants showed higher removal torque values. Interestingly, 3 smooth surface implants (16.6%) failed to osseointegrate, while all rough surface implants integrated successfully. Davies studied the mechanisms of

endosseous integration and concluded that outcomes would be critically dependant on implant surface characteristics (Davies 1998).

2.6.5   Early Implant Failure

Implant failures may be classified as being early or primary, when the implant fails to osseointegrate with the surrounding bone after implant placement, and secondary or late, after the implant has been loaded.

Friberg et al. (1991) carried out a retrospective analysis of 4,641 Brånemark dental implants placed from 1986-1988. The implants were followed to completion of prosthetic restorations. Sixty nine implants (1.5%) failed to osseointegrate and were mostly seen in completely edentulous maxillae in which the bone was poor both in quality and volume, and among short 7mm implants. Also, the majority of mobile implants were recorded at 2nd stage surgery, 48/69. It is worth noting that the implants used in this study were machined or smooth surface implants.

Esposito et al. (1998) reviewed the biological factors contributing to failures of osseointegration of dental implants and identified the following factors as the most common causes of early implant failure, excessive surgical trauma together with an impaired healing ability, premature loading and infection. Sennerby and Roos (1998) identified poor bone quality and the use of short implants in the atrophic maxilla, irradiation and bone grafting procedures of the atrophic maxilla as risk factors for early implant failure. Preiskel and Tsolka (1995) carried out a retrospective review and observed operator experience

with dental implants to have a major impact on the failure probability of unloaded implants. Sverzut et al. (2008) carried out a retrospective study to assess the influence of tobacco on early implant failure, but failed to find any difference between early implant loss for the smoking group versus the non smoking group, 2.81% and 3.32% respectively.

In a review published by O'Mahoney and Spencer (1999) no single aetiological factor was identified, however, causes for early implant failure included poor surgical technique, host factors that impair healing, and poor bone quality.

2.7 Infection Rates in Oral Surgery

Incidences of infection in dentoalveolar surgery are not well documented. Most published data pertains to third molar surgery which is a procedure with quite some variability in its invasiveness. The most common problem however, is confusing the acute inflammation of traumatic origin with wound infection. The incidence of wound infection following third molar removal, whether using antibiotic prophylaxis or not, is reported in the range of 1-27% (Curran et al. 1974; Hochwald et al. 1983; Mitchell 1986; Chiapasco et al. 1993). This results in an overall incidence of 3-5%. Studies comparing the use of prophylactic antibiotics to no antibiotics in third molar surgery report no statistical significance (Happonen et al. 1990; Sekhar et al. 2001; Poeschl et al. 2004). One retrospective study did however show statistically significant benefit in using prophylactic antibiotics in deep bone impactions (Piecuch et al 1995). The use of antibiotic prophylaxis for third molar removal has become

controversial, with their use not preventing the risk of undesirable outcomes (Martin et al. 2005).

Although prophylactic antibiotics have been advocated to reduce pain and swelling and to improve wound healing and treatment outcomes following gingivectomy (Stahl et al. 1969), osseous resective surgery (Ariaudo 1969; Kidd & Wade 1974), regenerative surgery (Cortellini & Bowers 1995; Machtei & Schallhorn 1995) and implant related surgery (Dent et al. 1997; Laskin et al. 2000), only few studies have attempted to determine the actual prevalence of post-operative infection following periodontal surgery with and without the use of prophylactic antibiotics.

Antibiotic prophylaxis has not been shown to provide any advantage in preventing post-operative infections or affecting the outcomes of periodontal surgery including gingivectomy (Pack & Haber 1983), mucogingival and osseous resective surgery (Ariaudo 1969; Pendrill & Reddy 1980; Appleman et al. 1982; Checchi et al. 1992), osseous grafts (Pack and Haber 1983) and also the surgical placement of dental implants (Gynther et al. 1998).

Infection rates following periodontal surgery when no antibiotics were used have been reported to be low, ranging from less than 1% (Pack & Haber 1983) to 4.4% (Checchi et al. 1992) for routine periodontal surgery and 4.5% following implant surgery (Gynther et al. 1998).

2.8 Pain Following Oral Surgery

Oral surgery is a common procedure that is rarely life threatening, however its' physical and psychological effects mean it still remains a stressful experience and a barrier to seeking dental care (Eli et al. 2003). While there are many studies on pain associated with the surgical removal of teeth, very little data exists on pain experience following placement of dental implants. Hashem et al. (2006) describes the pain following dental implant placement to be mild to moderate in nature.

It is clear that various factors such as previous negative dental experiences may influence patients' perception of pain during dental treatment (Locker et al. 1996). Other factors which may influence pain perception include anxiety, patient' expectations, anticipation of stress and control of the environment (Dworkin & Chen 1982). Indeed some studies report higher levels of anxiety among women as compared to men (Frazer & Hampson 1988; Eli et al. 2003). It has been reported that when anxiety exists, one is more perceptive of the pain from noxious events such as dental implant placement (Weisenberg 1977, von Graffenried et al. 1978). Oral surgery is both a stressful and anxiety producing procedure in dentistry and management of patients' anxiety is central to patients' pain control (Eli et al. 1997).

Tissue damage produced during surgery releases chemicals that initiate inflammatory pain by activating and sensitising nerve and fibre receptors (Loeser & Melzack 1999). These chemicals include serotonin, bradykinin, histamine and prostaglandins (Dray 1997).

Paracetamol (acetaminophen) is a non-opoid analgesic possessing antipyretic activity and is effective in relieving pain with a low incidence of adverse effects (Moore et al. 2000). It has been shown to be an effective analgesic in the control of post-operative dental pain in a number of clinical trials (Bentley & Head 1987; Mehlisch 1990; Kiersch et al. 1994). Ibuprofen is one of the most commonly prescribed non steroidal anti-inflammatory drugs (NSAIDs) for dental pain and has been shown to be effective in controlling post-operative dental pain pain in a number of clinical trials (Winter et al. 1978; Seymour et al. 1998). Both ibuprofen and paracetamol are amongst the most commonly used analgesics and are widely available without prescription around the world. Paracetamol is of particular value when NSAIDS are contraindicated, perhaps by known hypersensitivity or a history of gastrointestinal ulceration or bleeding (Nguyen et al. 1999).

While most studies looking at pain following oral surgery have focused their attention on third molar surgery, its various approaches such as raising a lingual flap or bone removal with the use of chisels or burs, very little data exists on the influence of antibiotics on pain following dentoalveolar surgery.

Hashem et al. (2006) conducted a prospective study to assess pain and anxiety following dental implant placement. 18 patients undergoing implant placement were instructed to keep recovery diaries to assess pain experience, limitation of activities and post-operative symptoms and to record average pain, worst pain and interference with daily activities using visual analogue scale questionnaires. Patients were also asked to complete the Splielberger self-evaluation questionnaire to assess anxiety. Cortisol levels were measured from

saliva samples again to assess anxiety 1 week prior to the surgery, on the day of surgery, 3 and 6 days post-operatively. Following implant placement most patients reported mild to moderate interference with daily activities and post-operative symptoms. Average pain experience decreased significantly with time ($p<0.001$). Worst pain ($p<0.001$) and limitation of daily activities ($p<0.001$) also decreased with time to about half the maximum level by the second or third day. Anxiety state was highest on the day of surgery, however the salivary cortisol level did not validate this as it did not differ with the time of collection ($p=0.075$). The authors concluded that implant placement is a mild to moderately painful and anxiety producing procedure and that some limitation of daily activities and post-operative symptoms are expected to occur, especially during the first 3 post-operative days.

Shugars et al. (1996) used similar methods to Hashem et al. to evaluate pain after surgical removal of third molar teeth. The VAS scores were mild for implant surgery (Hashem et al. 2006) compared to third molar removal (20 versus 48 for average pain; 22.5 versus 81 for worst pain; and 21 versus 78 for interference with daily activities).

It has been shown in multiple studies on surgical removal of third molars that there was no significant relationship between the operative trauma as measured by the duration of surgery and the magnitude of the post-operative pain experienced (Seymour et al. 1983; 1985).

2.9 Antibiotic Prophylaxis Regimens

Different anti-microbial prophylaxis protocols have been employed for the surgical placement of dental implants. The three main variables in each of these protocols have been:

1. Choice of drug.

2. Dose of drug.

3. Time-point of administration.

It is clear that the anti-microbial chosen should be effective against the bacteria causing any infection. These bacteria include aerobic streptococci, anaerobic gram-positive cocci and anaerobic gram-negative rods. Also the anti-microbial should be bactericidal and non-toxic. Taking these guidelines into consideration, penicillin is the first choice anti-microbial for prophylaxis in dental implant surgery (Peterson 1990; Page et al. 1993).

It is important also that the dose of the anti-microbial is sufficient so that the therapeutic level in the tissue is high enough to be effective against the causative bacteria. The various dosages employed follow one of the following four categories: American Heart Association guidelines for prevention of bacterial endocarditits 1990, 3 grams amoxicillin; American Heart Association guidelines for prevention of bacterial endocarditis 1997, 2 grams amoxicillin; Peterson's guidelines, twice the therapeutic level or greater; and any other dose (Dajani et al. 1990; Peterson 1990; Wilson et al. 2007).

When considering the time point of administration, the goal of anti-microbial prophylaxis is to provide a therapeutic level in the tissue when the bacterial

contamination occurs. It has been shown that antibiotics delayed for three hours are not more effective than no antibiotics at all. Also, antibiotic administration after surgery does not decrease the incidence of wound infection. It is thus clear that the use of prophylactic anti-microbials is limited to the intra-operative period (Burke 1961; Stone et al. 1979; Dajani et al. 1990; Page et al. 1993).

While there is limited data on the use of prophylactic antibiotics in dental implant surgery, there are some well designed studies on the influence of prophylactic antibiotics on surgical removal of impacted mandibular third molars. Sekhar et al. (2001) tested the efficacy of two different prophylactic regimes during the removal of impacted mandibular third molars from 151 patients using a prospective randomised placebo controlled study design. Patients were randomly assigned into one of three groups, placebo group, metronidazole 1g orally one hour pre-operatively, and metronidazole 400mg orally three times daily for 5 days post-operatively. Patients were assessed after 2 and 6 days for pain and after 6 days for swelling and reduction in mouth opening. There were no significant differences between the three groups (p=0.09). The authors concluded that antimicrobial prophylaxis pre-operatively or post-operatively, does not seem to reduce morbidity after removal of impacted mandibular third molars.

In a recent review article by Lawler et al. (2005) antibiotic prophylaxis was not recommended or required for most dentoalveolar procedures in fit and healthy individuals.

2.9.1 Antibiotic prophylaxis regimens for Dental Implant Surgery

In P.I. Brånemark's book "Tissue Integrated Prostheses", antibiotics were recommended pre-operatively and up to 10 days post-operatively. One of the most commonly followed protocols is the oral administration of 2g phenoxymethylpenicillin (penicillin V) about 1 hour pre-operatively and then 2g twice a day for ten days (Adell et al. 1985).

Later protocols recommended short-tem prophylaxis using either 2g penicillin-V, amoxicillin, or co-amoxiclav administered per os 1 hour pre-operatively and 500mg of penicillin-V four times daily for 1 day post-operatively (Flemmig & Neuman 1990).

Larson and McGlumphy (1993) in one of the earlier studies evaluated 125 patients who had 445 implants placed. All patients were given pre-operative penicillin and were then followed up for 12 weeks. Wound dehiscence was found in three patients but there was no evidence of infection. The authors concluded that pre-operative antibiotic prophylaxis is sufficient to prevent wound infection following placement of dental implants, however there was no control group included and therefore it was not possible to determine whether the results would have been different without such treatment.

Peterson carried out a prospective study to determine the effectiveness of pre-operative administration of antibiotics (Peterson et al. 1996). One thousand and twenty implants were placed in 270 patients. Three patients (1.1%) had post-operative infections which were resolved with antibiotics. Six implants (0.4%)

in 4 patients were not osseointegrated at 2nd stage surgery after 4 months. The very low rate of post-operative infection comparable to infection rates of clean surgery and the low incidence of implant failure at second stage surgery, show that the use of pre-operative antibiotic prophylaxis is effective. However the study did not include a control group and therefore it was not possible to determine if the results would have been different without the pre-operative antibiotics.

As part of the Dental Implant Clinical Research Group (DICRG) in the USA, Dent et al. (1997) carried out a prospective multi-centre clinical study to examine the influence of various antibiotic prophylaxis protocols. Whilst this study was prospective, the use of antibiotic which included the choice of drug, dose and time-point of administration was left to the surgeons' discretion. It therefore does not adhere to the strict randomised controlled trial guidelines. A total of 2,641 implants were placed and of these, 1,448 (55%) were placed in patients who had received prophylactic pre-operative antibiotics and 1,193 (45%) were placed in patients who did not receive any antibiotic coverage. The first comparison showed that significantly fewer failures occurred when pre-operative antibiotics were used ($p<0.001$), 1.5% failure with the use of pre-operative antibiotics versus 4.0% failure when no pre-operative antibiotic was used. The second comparison between pre-operative antibiotics used at a dose according to Peterson's criteria or greater versus pre-operative antibiotics used at a dose less than Peterson's criteria failed to show any significance. The third comparison showed that significantly fewer failures occurred when pre-operative antibiotics were used at a dose according to the American Heart Association guidelines for bacterial endocarditis 1990, 1.4%, versus pre-

operative antibiotics used at a lower dose, 3.3% ($p<0.005$). Also, the use of post-operative antibiotics was shown to have no effect on the outcome on post-operative infection and implant survival (Dent et al. 1997).

In a controlled retrospective study, Gynther et al. (1998) compared two groups of patients treated with dental implants. The first group consisted of 147 patients who had 790 implants placed, were treated between the years 1980 to 1985 and received 1g of phenoxymethyl penicillin pre-operatively and 1g 8 hourly post-operatively for ten days. They compared this group to a second group consisting of 132 patients who had 664 implants placed, were treated between the years 1991 to 1995 and received no pre- or post-operative antibiotics. They found no significant difference with respect to post-operative infection and implant survival between the two groups, concluding that prophylactic antibiotics had no effect on minimizing infection rates after implant surgery (Gynther et al.1998).

As part of the Dental Implant Clinical Research Group (DICRG) in the USA, Laskin et al. (2000) studied the influence of pre-operative antibiotics on the long- term success of endosseous implants at 36 months. A retrospective multi-centre study was carried out. The use of pre- or post-operative antibiotics, the choice of drug and the dosage was left to the surgeons' discretion. Data for 2,973 implants were recorded and correlated with failure of osseointegration at the following four stages, during healing (Stage 1), at second stage surgery (Stage 2), prior to loading (Stage 3), and from loading to 36 months (Stage 4). Pre-operative antibiotics were administered in 387 patients who had 1,743 implants placed. No pre-operative antibiotics were administered in 315 patients

who had 1,287 implants placed. In total, 96% of patients received post-operative antibiotics. Comparisons were based upon three groups, patients who had no pre-operative antibiotics, patients who received pre-operative antibiotics according to Peterson's criterion and patients who received pre-operative antibiotics according to the American Heart Association guidelines for prophylaxis against bacterial endocarditis, 1990. The use of pre-operative antibiotics was found to significantly ($p<0.05$) improve implant survival compared to no pre-operative antibiotic usage, 4.6% failure compared to 10% failure. Implants placed in patients who received pre-operative antibiotics according to the AHA guidelines had a higher overall survival rate than those in patients who received a smaller dose or no antibiotics at all, 95.3% compared to 92% ($p<0.05$). Implants placed in patients who received antibiotics according to Petersen's criterion had the highest overall survival rate, 95.7%, compared to those in patients who received a lower dose or no pre-operative antibiotics at all, 91.1% ($p<0.05$) (Laskin et al. 2000).

Esposito et al. (2003) conducted a review of the use of prophylactic antibiotics for dental implant placement. No randomised controlled trials were identified. The authors concluded that there was not appropriate scientific evidence to either recommend or discourage the use of prophylactic antibiotics to prevent complications and failures of dental implants.

In a prospective study carried out by Binahmed et al. (2005), the use of a single pre-operative antibiotic dose with no post-operative antibiotics was compared to the use of a pre-operative antibiotic dose and post-operative antibiotics for 7 days. In the trial, 445 implants were placed in 125 patients who received a

single pre-operative antibiotic dose and 302 implants were placed in 90 patients who received both pre- and post-operative antibiotics. Analysis of the results revealed no statistical difference between the two regimens used (p=0.56). Long-term prophylactic antibiotics did not reduce the incidence of post-operative wound infections and implant failure (Binahmed et al. 2005).

Recently, a well designed multi-centre placebo controlled randomised clinical trial was carried out by Esposito et al. (2008) to evaluate the efficacy of prophylactic antibiotics for dental implant placement. A total of 316 patients were evaluated, 158 patients received 2 grams of amoxicillin orally one hour pre-operatively and 158 patients received a similar placebo drug orally one hour pre-operatively. No post-operative antibiotics were administered. Four outcome measures were recorded, prosthesis failure, implant failure, post-operative biological complication and post-operative adverse events. Patients were followed up for four months. Prosthesis failure was higher for the placebo group, 4, than the antibiotic group, 2, however the difference was not statistically significant (p=0.68). Nine implants failed in 8 patients in the placebo group versus 2 implants in 2 patients in the antibiotic group, however the difference was not statistically significant (p=0.10). One adverse event occurred in each group. One week after implant placement 2 biological complications occurred in the placebo group and 4 in the antibiotic group, however the difference was not statistically significant (p=0.68). Two weeks after implant placement 1 biological complication occurred in each group. Four months after implant placement 2 biological complications occurred in the placebo group and 1 in the antibiotic group, however the difference was not statistically significant (p=0.62) (Esposito et al. 2008).

Abu-Ta'a et al. (2008) carried out a randomised controlled trial comparing the use of pre- and post-operative antibiotics to no antibiotics in dental implant surgery. A total of 80 consecutive patients were included, 40 received 1 gram of amoxicillin one hour pre-operatively and 2 grams of amoxicillin for two days post-operatively, and 40 received no antibiotics. Bacterial samples were taken from the peri-oral skin in all patients and from the nares in 12 patients. Patients' subjective experience of discomfort was recorded using visual analogue scale questionnaires. Patients were followed up for 5 months. No prosthesis failed in either group. Five implants failed in 3 patients who did not receive antibiotics and whilst this was not statistically significant it tended towards significance. No adverse events were recorded. There were no significant differences between either group either for post-operative infections, or for microbiota. Patients from the antibiotic group had significantly less subjective perception of post-operative discomfort than the group who received no antibiotics (Abu-Ta'a et al. 2008).

Esposito et al. (2008) conducted meta analyses of the above two randomised controlled trials, Esposito et al. (2008), and Abu-Ta'a et al. (2008) with the following results. There were no significant differences for prosthesis failure, post-operative infection and adverse events. More patients experienced implant loss when no pre-operative antibiotics were administered and this was statistically significant with a risk ratio (RR) 0.22, 95% confidence interval (CI) 0.08 to 0.86. To illustrate the magnitude of the effect of implant failures, the number of patients needed to treat (NNT), i.e. given antibiotics to prevent one patient having an implant failure is 25 (95 % CI 13 to 100). This is based on a patient implant failure of 6% in patients not receiving antibiotics. The

meta-analyses also concluded that there are no trials determining which is the most effective antibiotic, dose, and duration (Esposito et al. 2008).

2.9.2   Aseptic Regimens in Dental Implant Surgery

Several sources of infection during surgery in the oral cavity have been identified, instruments, the hands of both surgeon and assistant, the air of the operating room, patients' nostrils, patients' saliva and the peri-oral skin (van Steenberghe et al. 1997).

The supine position of the patient and the use of two independent suction devices, one for the mouth and one for the surgical wound only, can decrease the chances of wound decontamination (van Steenberghe et al. 1997).

The use of a meshed nose guard can prevent contact with the highly contaminated nares and it was demonstrated that the expired air does not contain more bacteria than the surrounding air of the operating room (van Steenberghe et al. 1997). The main carriage sites of *Staphylococcus aureus* in healthy individuals are the nares. It has been reported that 20-30% of healthy individuals are nasal carriers (Ayliffe & Lowbury 1982) and that *S. aureus* carriers have a two- to nine-fold increased risk of developing wound infections (Wenzel & Perl 1995).

In a study designed to examine the effect of surgical scrubbing and skin disinfection with the use of povidone-iodine in orthopaedic surgery, Salvi et al. (2006) observed pre-surgical disinfection of the patients' skin to be completely

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effective with 100% of samples negative for microbes. However, surgical scrubbing of the surgeons' hands was observed to be insifficient in completely eliminating bacterial contamination.

During intra-oral surgery, reduction of salivary flow can be achieved by atropine and of the microbial flora by pre-operative rinsing with chlorhexadine (Altonen et al. 1976; Veksler et al. 1991). Altonen et al. (1976) tested the use of two mouthrinses, 1% povidone-iodine and 0.2% aqueous solution of chlorhexadine gluconate for their degerming effect on saliva. They found that chlorhexadine reduced the bacterial count more than the povidone-iodine by about one logarithim and that the effect was also of longer duration. Veksler et al. (1991) examined the effect of 0.12% chlorhexadine gluconate mouth rinse compared to a control of sterile water. They observed an immediate reduction in salivary bacterial load of 97% with the use of 0.12% chlorhexadine gluconate mouthrinse.

Rinsing the oral cavity with chlorhexadine gluconate (0.12%-0.2%) for one minute is advocated prior to implant surgery (Buser et al 2000). Also, disinfection of the perioral skin prior to the surgery and the use of sterile drapes are recommended (Buser et al. 2000). It has been demonstrated however, that aseptic operatory conditions are not necessary for successful implant integration to occur (Scharf & Tarnow 1993). It has also been reported that the use of chlorhexadine gluconate 0.12% in the peri-operative period resulted in a significant reduction in the incidence of infective complications and this in turn resulted in a significant difference in implant survival (Lambert & Morris 1997).

2.10 Literature review conclusions

Following a review of the current literature it can be concluded that dental implants may fail to osseointegration resulting in early or primary implant failure. It is apparent that this can be influenced by a number of variables including aseptic surgical technique, atraumatic surgical technique, poor bone quality and impaired host immunity. The influence of pre-operative antibiotic prophylaxis on osseointegration of dental implants has been controversial. At the conception of this trial no randomised controlled trials assessing the influence of pre-operative antibiotic prophylaxis had been published and therefore no evidence based recommendations could be made. Esposito et al. published a meta-analysis in 2008 of the only two randomised controlled trials and concluded that pre-operative antibiotic prophylaxis may result in higher rates of successful osseointegration. It was also concluded that there was no evidence to support one antibiotic over another and at what dose. The influence of pre-operative antibiotic prophylaxis on post-operative morbidity, pain and interference with daily activities has scarcely been investigated. Dental implant surgery has been identified as a moderately painful event and it would therefore be of interest to assess the effect of prophylactic antibiotics on post-operative pain.

3. Materials and Methods

3.1 Study Design

The design of the study is a prospective double blind placebo controlled randomised clinical trial. The patients were randomly assigned to the antibiotic test group (N=27) and placebo control group (N=28).

3.2 Population Sample

The patients were selected from a population on the implant waiting list at the department of Restorative Dentistry and Periodontology, Dublin Dental School and Hospital. Those consecutively treated patients that comply with both the inclusion and exclusion criteria and who have signed consent for participation in the study will form the study sample.

Twenty seven patients were included in the antibiotic test group and 28 patients were included in the placebo group. These subjects comprised a composite of those studied by Dr. Maher Kemmoonna in a previous thesis in 2007 (N=29) and those from the present continuation study (N=26).

Sample size	55
Control (antibiotic) group	27
Test (placebo) group	28

Table 3.1   Population sample

3.3 Inclusion Criteria

The following inclusion criteria must be present in order for the patient to be included in the study.

1. Presence of a partial edentulous or edentulous alveolar ridge.

2. Presence of a tooth or several teeth regarded as non-restorable with the intention of immediate implant placement.

3. Periodontal healthy remaining dentition.

4. Presence of a non-infected surgical site.

3.4 Exclusion Criteria

Exclusion criteria for the patients are medical conditions that require antibiotic premedication such as prosthetic heart valve replacement, skeletal joint replacement, previous history of infective endocarditis and a history of rheumatic fever. Furthermore, patients with metabolic disease such as type one or two diabetes mellitus, patients with past and present neo-plastic disease, previous radiotherapy in the head and neck area, immunosuppressed patients and those patients with blood coagulation impairment. Also excluded are those patients with a history of systemic steroid medication or recent systemic antibiotic therapy. Pregnant and lactating women and patients with allergy to the antibiotic chosen will be excluded. In order to be able to accurately obtain information on a patients' pain experience during and after the surgery, patients taking regular analgesics and antidepressants will also be excluded.

Those patients who require a simultaneous bone graft or soft tissue graft at the time of implant placement will be excluded. The influence of the bone grafting materials and the added surgical procedure cannot be quantified or eliminated. Patients who are not able to attend for the 2nd day and 7th day post-operative visits will also be excluded.

3.5 Consent

Oral and written consent needs to be provided by the patients in the sample group prior to participation in the clinical study. Patients will receive a written statement of the nature of the study at the first visit and then given time before the surgical appointment to make their decision on participating in the study. Patients will be informed that declining to participate in the study will not affect their treatment course. Patients will be previously informed of the surgical aspect and post-operative risks of implant placement. The patients will sign a written consent form as presently used in the hospital regarding the actual surgery.

3.6 Randomization

Every patient will be randomly assigned to one of the following two groups:

1.   Test group – 3g Amoxicillin orally prior to the surgery.

2.   Control group – Placebo orally prior to the surgery.

Consecutively treated patients will receive consecutive numbers correlating with the number of an envelope. This envelope will contain either the 3g Amoxicillin, or a similar placebo drug. A master file will hold the key to whether an envelope contains the 3g Amoxicillin or the placebo drug.

3.7 Blindness

An independent person will administer the antibiotic or the placebo. Neither the surgeon nor the patient will know which has been taken in order to ensure a double blind approach.

3.8 Operators

The students participating in the three year doctorate course in Periodontology at the Dublin Dental School and Hospital will be the clinicians carrying out the surgery. These students will be at different stages of their training, and will have different levels of experience. All surgery will be supervised by a clinical lecturer in periodontology.

3.9 Implant Systems

Implants used will be those that are currently used in the hospital and include:

1. Osseotite® and OsseotiteNT®, Biomet3i, Florida, USA.

2. Brånemark® TiUnite™ MKIII and MKIV, Nobel Biocare, Sweden.

3. Ankylos®, Dentsply Friadent, Germany.

4. Straumann® SLA, Straumann Implants, Switzerland.

The choice of implant system will be made on a case by case basis by the operating clinician with the aid of the supervising clinical lecturer.

3.10 Surgical Procedure

Implants will be placed according to the manufacturers guidelines using standard surgical procedures. Patients will rinse with a chlorhexadine 0.2% mouthrinse for at least 30 seconds prior to the surgery. Local anaesthetic used will be xylocaine 2% with adrenaline 1:80,000.

Following adequate local anaesthesia, a mucoperiosteal flap will be raised with or without one or two relieving incisions as determined by the local anatomy,

including availability of bone, presence of neighbouring tooth roots and aesthetics. The use of a surgical stent will depend on the case and restorative planning required for it. Osteotomy will then be carried out under copious saline irrigation according to the guidelines set out by each individual implant company. Implants will then be placed with a view to obtaining good primary stability. A decision will then be made between placing a cover screw and opting for a two stage approach, or a healing abutment and a one stage approach.

If a dehiscence or fenestration should result after the insertion of the dental implant and augmentation of the bone is indicated, then the patient will be excluded from the data analysis and a post-operative antibiotic will be prescribed.

Closure of the surgical site with either resorbable or non-resorbable sutures will then be performed ensuring tension free closure of the flaps.

Radiographs are then necessary to assess the position of the implant within the bone.

3.11 Post-operative Procedures

The patient will be personally instructed and handed out standardized forms on post-operative care. Patients will be advised on the use of post-operative pain medication. To minimise the influence of independent variables, all patients will be instructed to use paracetamol 500mg tablets as required to a maximum

of 4g per day. The patient will be asked to keep a pain medication diary accounting for the number of paracetamol 500mg tablets taken for the first post-operative week.

Patients will be advised to remain on a soft diet for the first post-operative week. Patients will be instructed to use a chlorhexadine 0.2% mouthwash 4 to 5 times daily for the first post-operative week.

3.12 Outcome Variables

Recordings of outcome variables as described below will be obtained at the 2nd and 7th post-operative day. Recordings of osseointegration failure or success will be recorded four months post-operatively or at 2nd stage surgery.

Information will be collected on the 'data collection sheet dentist' and the 'data collection sheet patient', as shown in the appendix.

3.12.1 Post-operative swelling

Post-operative swelling will be recorded on the 2nd and 7th days. Two independent examiners will grade the existing swelling, and make a decision of severity on an agreement basis.

0 = No swelling

1 = Mild swelling

2 = Moderate swelling

3 = Severe swelling

3.12.2 Post-operative bruising

Post-operative bruising will be recorded on the 2nd and 7th days by 1 and the same examiner using Boolean Variables.

0 = None

1 = Present

3.12.3 Post-operative suppuration

Post-operative suppuration will be recorded on the 2nd and 7th days by 1 and the same examiner using Boolean Variables.

0 = None

1 = Present

3.12.4 Post-operative wound dehiscence

Post-operative wound dehiscence will be recorded on the 2nd and 7th days by 1 and same examiner using Boolean Variables.

0 = None

1 = Present

3.12.5 Patients' pain experience

The patient's pain experience described as the 'worst pain' will be recorded using a 100 mm visual analogue scale questionnaire with endpoints marked as 'no pain' and 'intolerable pain'. This will be recorded by the patient for the surgical procedure and daily thereafter for 7 days.

The patient will be informed that the information given in the visual analogue scale pain diary will not be accessible by the surgeon who carried out their procedure in order to prevent bias.

The patient's pain experience expressed as the number of paracetamol 500mg tablets taken post-operatively will be recorded for 7 days.

3.12.6 Interference with daily activities

Patient's experience of the interference with their daily activities will be recorded using a 100mm visual analogue scale questionnaires with endpoints marked as 'none' and 'extremely much'. This will be recorded by the patient daily post-operatively for seven days. Daily activities for the patient include their ability to chew the foods they wanted to, their ability to open their mouth wide, talk and carry out conversations, sleep, go to school or work, carry on a regular social life and participate in their favourite recreational activities.

3.12.7 Osseointegration

Osseointegration of the implant will be recorded after 4 months by 2 independent examiners.

Success = Immobile

Failure = Mobile

This will coincide with the 2nd stage surgery of the implant for 2 stage surgical approaches. For 1 stage surgical approaches, this should coincide with taking an implant level impression for restoration of the implant.

3.13 Factors Related to the Outcome Variables

3.13.1 Factors to be recorded and related to all outcome variables:

1. Length of incision.

2. Duration of surgery.

3.13.2 Factors to be recorded and related to osseointegration of the implants only:

1. Smoking habits.

2. Implant system.

3. Site of implant.

4. Surgical approach.

5. Number of implants placed.

6. Previous bone augmentation.

7. Operator.

3.14 Statistical Analysis

Due to the non-parametric nature of the data collected, the following statistical analyses will be carried out, Pearson's Chi Square test, Fisher's Exact test, Wilcoxon test, Kruskal-Wallis test and Spearman's rank correlation test.

3.15 Patient Dropout

In the case of a patient initially thought not to require simultaneous bone grafting and having provided consent for participation in the study, where these patients intra-operatively are found to need bone grafting of any resultant fenestration or dehiscence, this patient will be prescribed post-operative antibiotics and excluded from the data analysis.

In the case of a patient presenting post-operatively in pain not related to the implant surgery, this patient will be excluded from the data analysis as these data would be inaccurate.

In the case of a patient presenting in pain to his or her doctor or dentist, they may also need to be excluded if additional pain medication or antibiotics were prescribed.

In the case of a patient not returning for his or her follow up appointments for assessment of the outcome variable, this patient will also be excluded due to incomplete data collection.

3.16 Ethical Approval

Ethical approval was sought from the Saint James Hospital and The Adelaide and Meath Hospital, Dublin Research Ethics Committee before commencement of the clinical study. Ethical approval was granted on the 22nd June, 2005, for the first part of the study when the main researcher was Dr. Maher Kemmoona. Ethical approval was granted on 14th October, 2007 for continuation of the study until June 2009 with the author as the main researcher.

3.17 Sequence of Patients' Visits

First Visit:

Clinical assessment will be carried out including any special tests and appropriate radiographs. Patients will receive a written statement of the nature of the study.

Second Visit:

Informed consent will be obtained for both participation in the clinical study and for the surgical procedure. Randomisation number will be allocated to the patient and the corresponding premedication will be administered. This will be followed by the surgical phase of treatment. Post-operative radiographs will be taken. Post-operative instructions will be explained. The researcher will record the factors to be related to the outcome variables. The patient will record the pain experience during surgery using a 100mm visual analogue scale questionnaire.

Third Visit:

The patient will attend 2 days post-operatively for recording of the outcome variables. Any unexpected post-operative complications can also be dealt with at this visit.

Fourth Visit:

The patient will attend 7 days post-operatively for recording of the outcome variables. Collection of the patient's daily pain and interference with activities diaries will also be collected. Suture removal will be performed at this visit.

Fifth Visit:

Three to four months post-operatively, 2nd stage implant surgery will be carried out for those implants where a 2 stage surgical approach was used. For patients where a 1 stage surgical approach was employed, implant level impressions will be taken to allow restoration of the implant to commence. The osseointegration of the implant will be assessed as determined by the stability and immobility of the implant when torque is applied.

3.18 Null Hypotheses

The first null hypotheses is that there would be no difference between either the control group, 3g amoxicillin administered pre-operatively and the test group, placebo drug administered pre-operatively, in the post-operative pain and morbidity of the implant surgery.

The second null hypotheses is that there would be no difference between either the control group, 3g amoxicillin administered pre-operatively and the test group, placebo drug administered pre-operatively in the osseointegration of the implant.

4. Results

4.1 Population sample demographics

A total Sample of 55 patients, (N=55) were enrolled. The control and test groups were not matched for age, sex or smoking status. However there did not appear to be any significant differences between the demographics of both the control ad test groups.

	Control (Antibiotic): 27	Test (Placebo): 28
Male	11	8
Female	16	20
<40	16	15
40-60	7	10
>60	4	3
Non smoker	20	22
Smoker	7	6

Table 4.0   Demographics of population study sample

4.2   Prophylactic medication on pain experience

4.1.1   Influence of prophylactic medication on pain experience during surgery

Figure 4.1 demonstrates the influence of prophylactic medication on pain experience during surgery for both groups. There was no statistically significant difference between the two groups (Wilcoxon p=0.74).
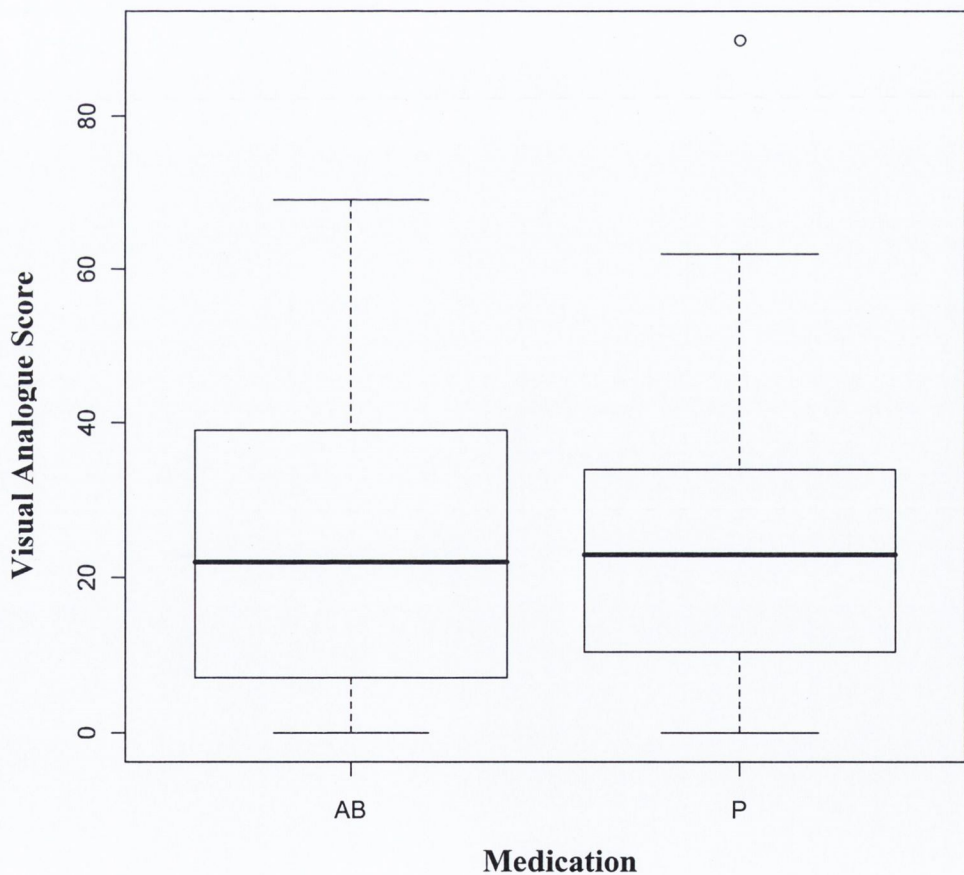
Fig. 4.1   Box plot comparing pain experience during surgery for both antibiotic and placebo groups using visual analogue scores on the Y-axis.

4.1.2 Influence of prophylactic medication on pain experience after 2 days

Figure 4.2 demonstrates the influence of prophylactic medication on pain experience after 2 post-operative days for both groups. There was no statistically significant difference between the two groups (Wilcoxon p=0.10).
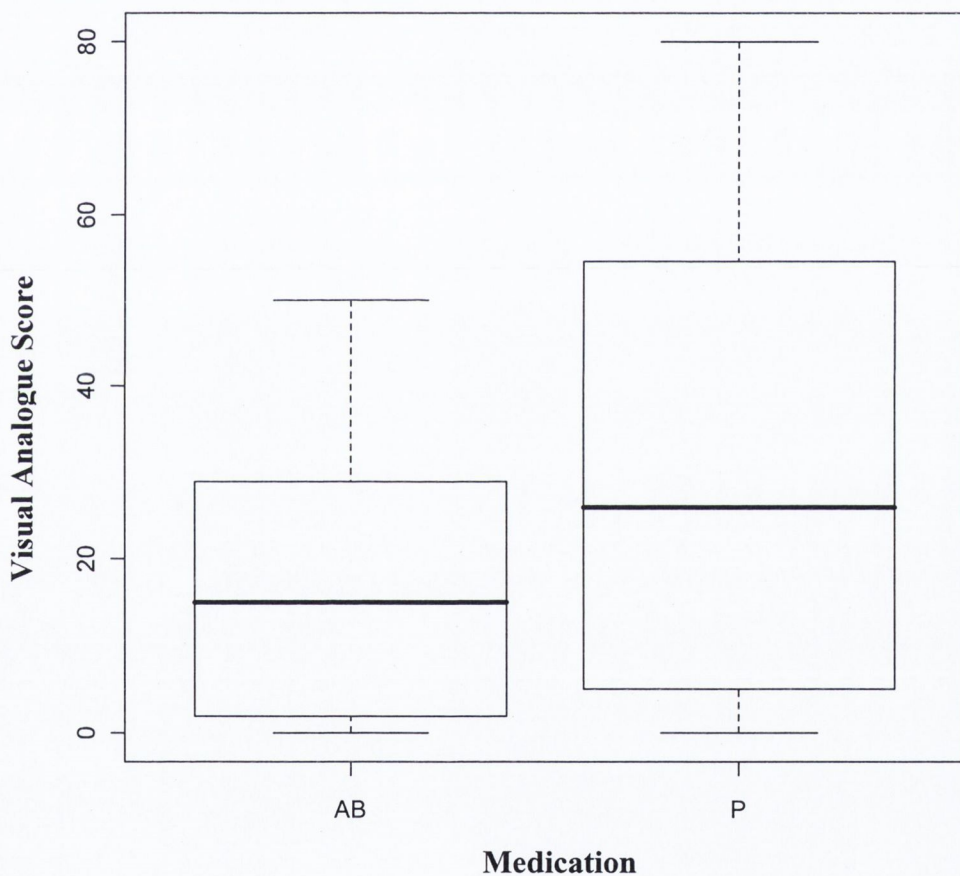
Fig. 4.2 **Box plot comparing pain experience after 2 days for both antibiotic and placebo groups using visual analogue scores on the Y-axis.**

4.1.3　Influence of prophylactic medication on pain experience after 7 days

Figure 4.3 demonstrates the influence of prophylactic medication on pain experience post-operatively after 7 days for both groups. The placebo group appeared to experience more pain after 7 days than the antibiotic group (Wilcoxon p=0.016).
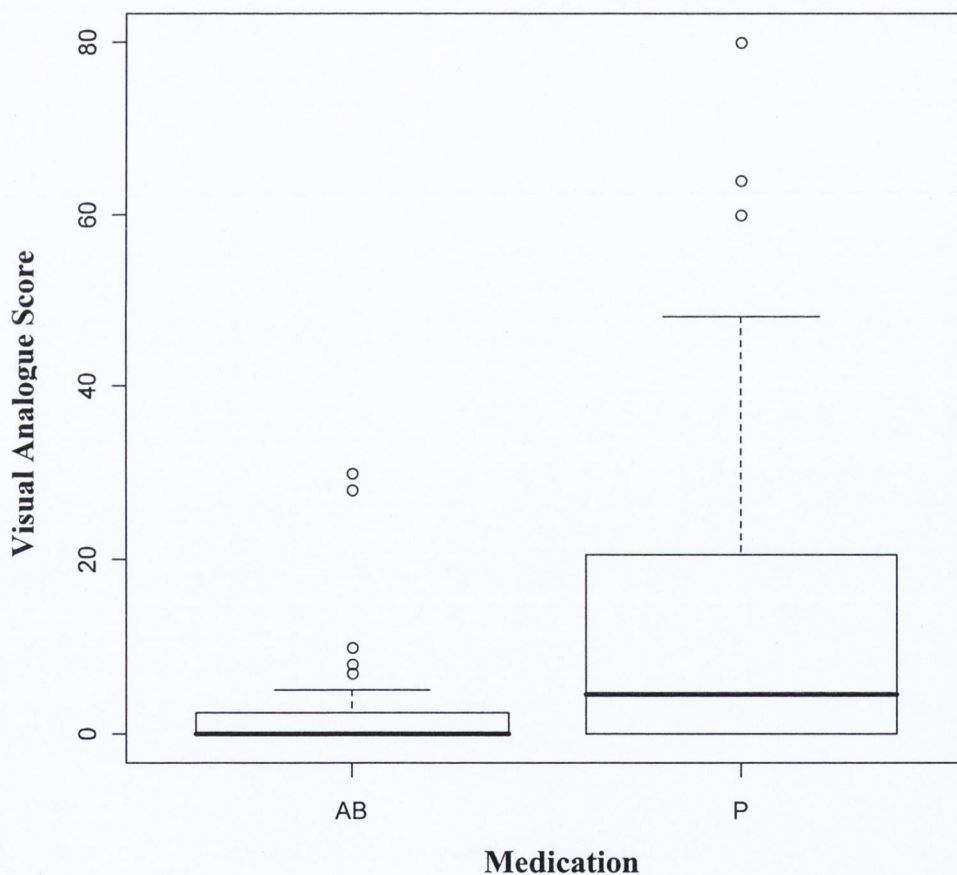
Fig. 4.3　Box plot comparing pain experience after 7 days for both antibiotic and placebo groups using visual analogue scores on the Y-axis.

4.1.4　Influence of prophylactic medication on pain experience represented by the number of analgesics taken after 7 days

Figure 4.4 demonstrates the influence of prophylactic medication on pain experience represented by the number of paracetamol 500mg tablets taken after 7 days. The placebo group appeared to experience more pain after 7 days than the antibiotic group (Wilcoxon $p=0.008$).
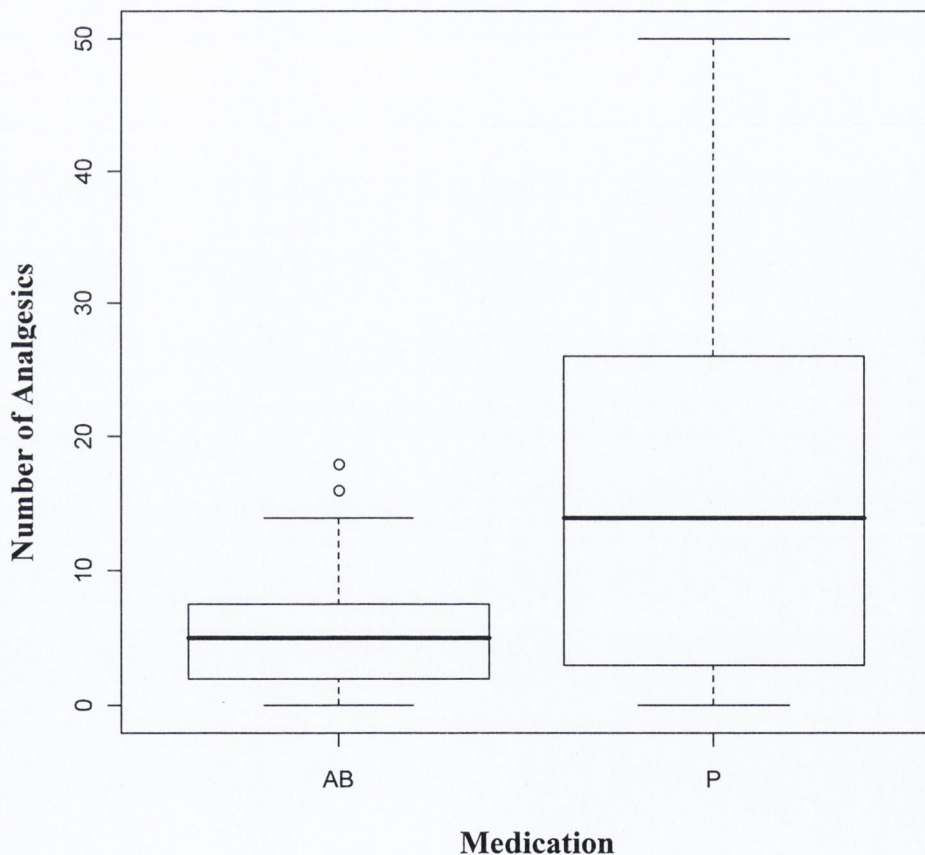
Fig. 4.4　　　**Box plot comparing pain experience after 7 days for both antibiotic and placebo groups represented by the number of paracetamol 500mg tablets taken.**

4.2 Prophylactic medication on daily activities

4.2.1 Influence of prophylactic medication on daily activities after 2 days

Figure 4.5 demonstrates the influence of prophylactic medication on daily activities after 2 days. There was no statistically significant difference observed between the two groups (Wilcoxon p=0.15).
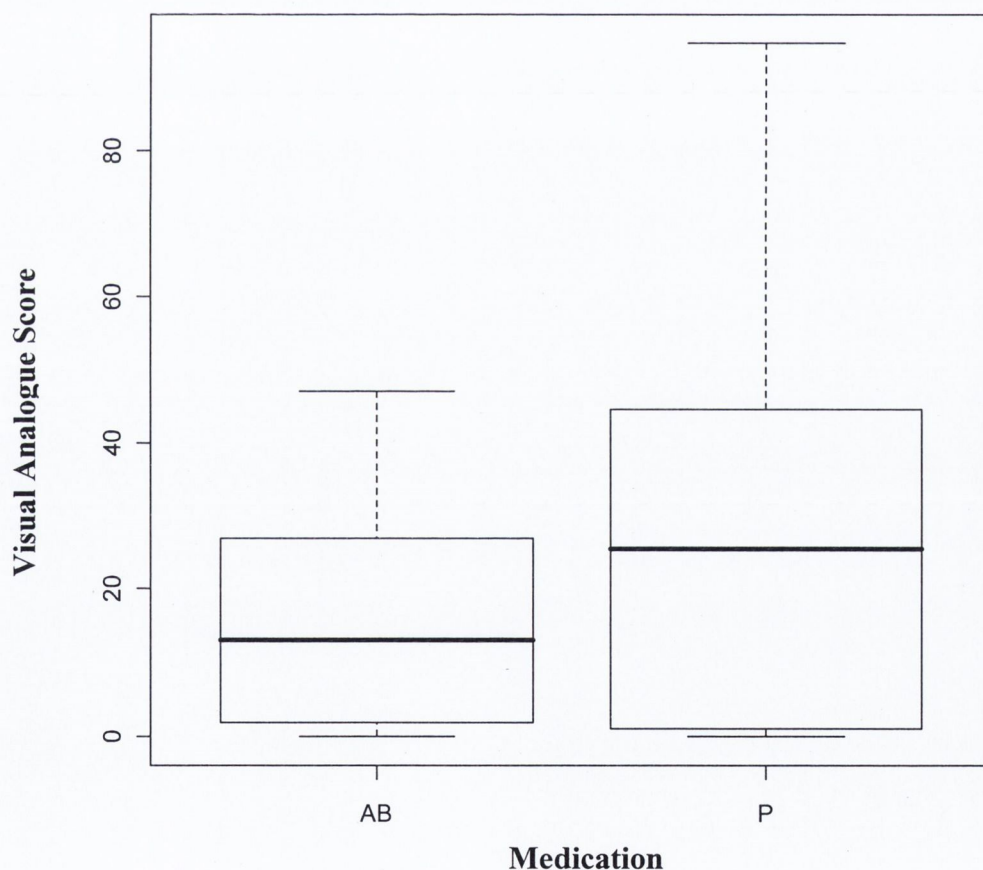
Fig. 4.5   **Box plot comparing interference with daily activities after 2 days for both antibiotic and placebo groups using visual analogue scores on the Y-axis.**

4.2.2 Influence of prophylactic medication on daily activitiesafter 7 days

Figure 4.6 demonstrates the influence of prophylactic medication on daily activities after 7 days. The placebo group appeared to experience more interference with daily activities after 7 days (Wilcoxon p=0.01).
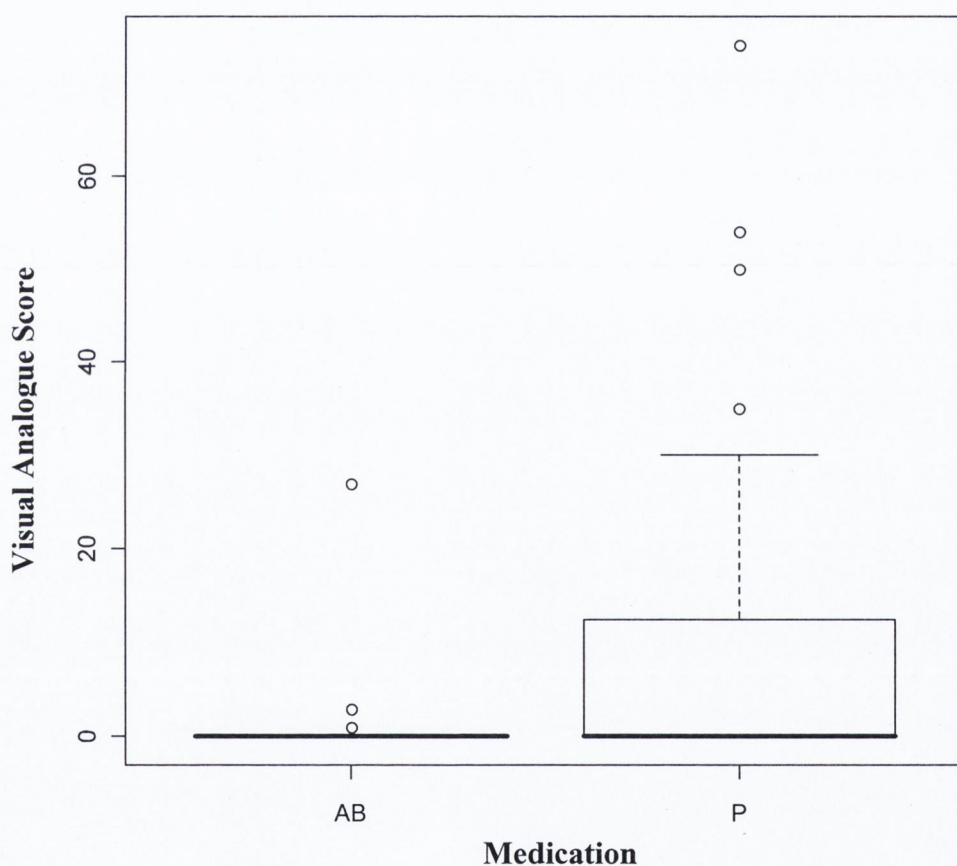
Fig. 4.6   Box plot comparing interference with daily activities after 7 days for both antibiotic and placebo groups using visual analogue scores on the Y-axis.

4.3 Prophylactic medication on osseointegration

Figure 4.7 demonstrates the influence of prophylactic medication on osseointegration at 2nd stage surgery. The placebo group appeared to experience a higher failure of osseointegration of dental implants (Fisher's Exact $p=0.05$).

Osseointegration	Antibiotics	Placebo
Yes	27	23
No	0	5

Table 4.1   Influence of prophylactic medication on osseointegration at 2nd stage surgery
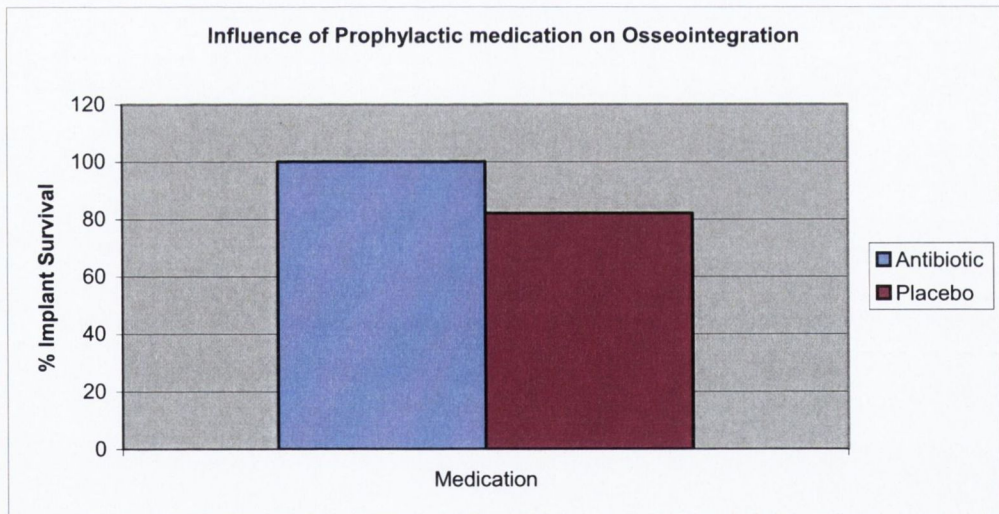
Fig 4.7   Influence of prophylactic medication on osseointegration at 2nd stage surgery.

4.4   Prophylactic medication on post-operative morbidity

4.4.1   Influence of prophylactic medication on post-operative swelling after 2 days

Figure 4.8 demonstrates the influence of prophylactic medication on post-operative swelling after 2 days. When the data was collapsed into a 2x2 table with no swelling versus mild, moderate or severe swelling, Fishers exact test revealed no statistically significant difference observed between the two groups.

Medication	No Swelling	Mild Swelling	Moderate Swelling	Severe Swelling
Antibiotic	8	14	4	1
Placebo	5	14	7	2

Table 4.2   Influence of prophylactic medication on post-operative swelling after 2 days

Fig 4.8   Influence of prophylactic medication on post-operative swelling after 2 days.

4.4.2 Influence of prophylactic medication on post-operative swelling after 7 days

Figure 4.9 demonstrates the influence of prophylactic medication on post-operative swelling after 7 days. When the data was collapsed into a 2x2 table with no swelling versus mild, moderate or severe swelling, Fishers exact test revealed no statistically significant difference observed between the two groups.

Medication	No Swelling	Mild Swelling	Moderate Swelling	Severe Swelling
Antibiotic	22	5	0	0
Placebo	18	7	2	1

Table 4.3   Influence of prophylactic medication on post-operative swelling after 7 days

Fig. 4.9   Influence of prophylactic medication on post-operative swelling after 7 days.

4.4.3 Influence of prophylactic medication on post-operative bruising after 2 days

Figure 4.10 demonstrates the influence of prophylactic medication on post-operative bruising after 2 days. The placebo group appeared to experience more post-operative bruising after 2 days (Fisher's Exact p=0.05).

Medication	Bruising absent	Bruising present
Antibiotic	26	1
Placebo	21	7

Table 4.4   Influence of prophylactic medication on post-operative bruising after 2 days
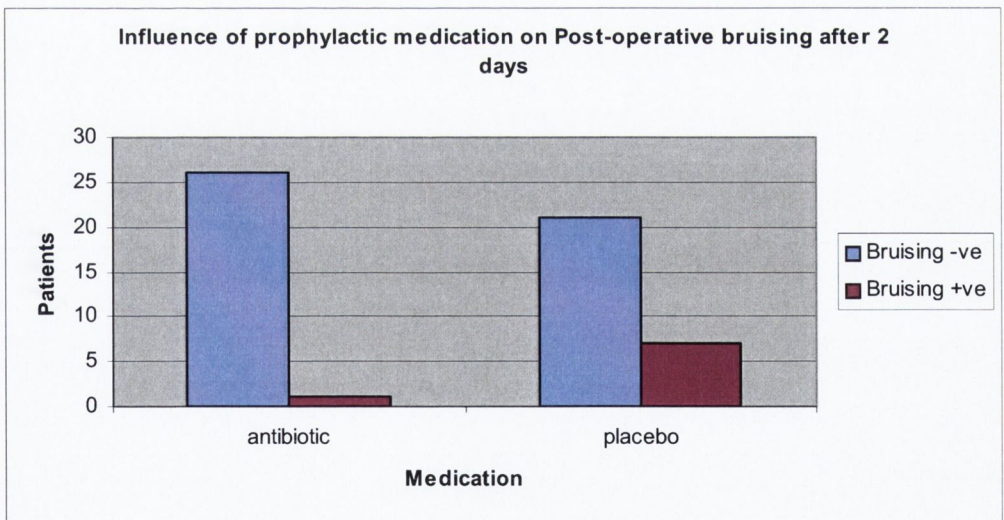
Fig. 4.10   Influence of prophylactic medication on post-operative bruising after 2 days.

4.4.4 Influence of prophylactic medication on post-operative bruising after 7 days

Figure 4.11 demonstrates the influence of prophylactic medication on post-operative bruising after 7 days. The response was similar for both groups.

Medication	Bruising absent	Bruising present
Antibiotic	27	0
Placebo	27	1

Table 4.5 **Influence of prophylactic medication on post-operative bruising after 7 days**
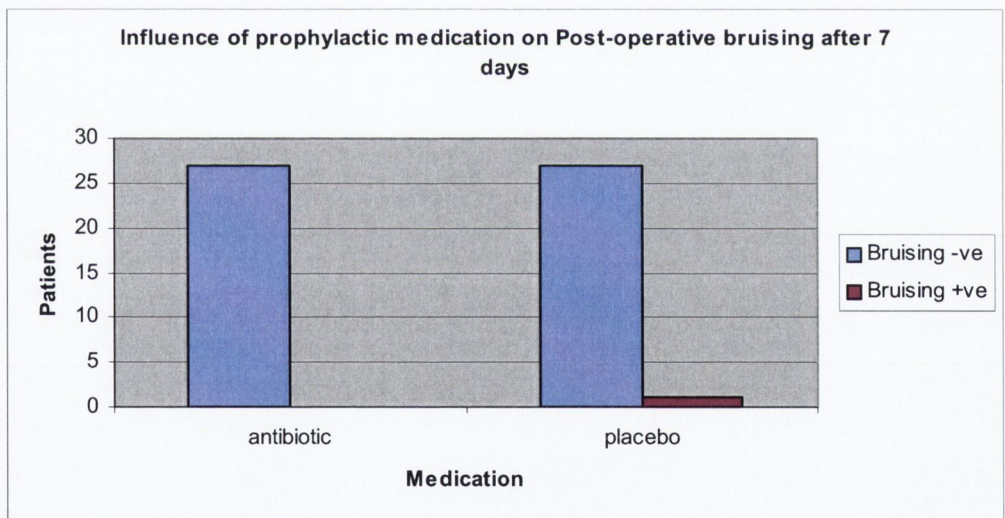
Fig. 4.11 **Influence of prophylactic medication on post-operative bruising after 7 days.**

4.4.5 Influence of prophylactic medication on post-operative wound dehiscence after 2 days

Figure 4.12 demonstrates the influence of prophylactic medication on post-operative wound dehiscence after 2 days. The response was similar for both groups

Medication	No wound dehiscence	Wound dehiscence present
Antibiotic	26	1
Placebo	27	1

Table 4.6   Influence of prophylactic medication on post-operative wound dehiscence after 2 days
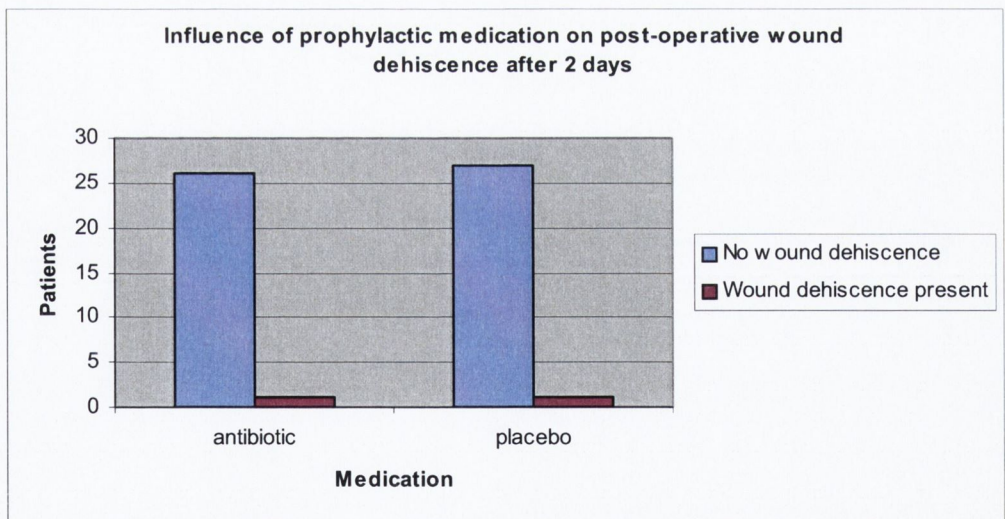
Fig 4.12   Influence of prophylactic medication on post-operative wound dehiscence after 2 days.

4.4.6 Influence of prophylactic medication on post-operative wound dehiscence after 7 days

Figure 4.13 demonstrates the influence of prophylactic medication on post-operative wound dehiscence after 7 days. The response was similar for both groups

Medication	No wound dehiscence	Wound dehiscence present
Antibiotic	25	2
Placebo	25	3

Table 4.7 Influence of prophylactic medication on post-operative wound dehiscence after 7 days
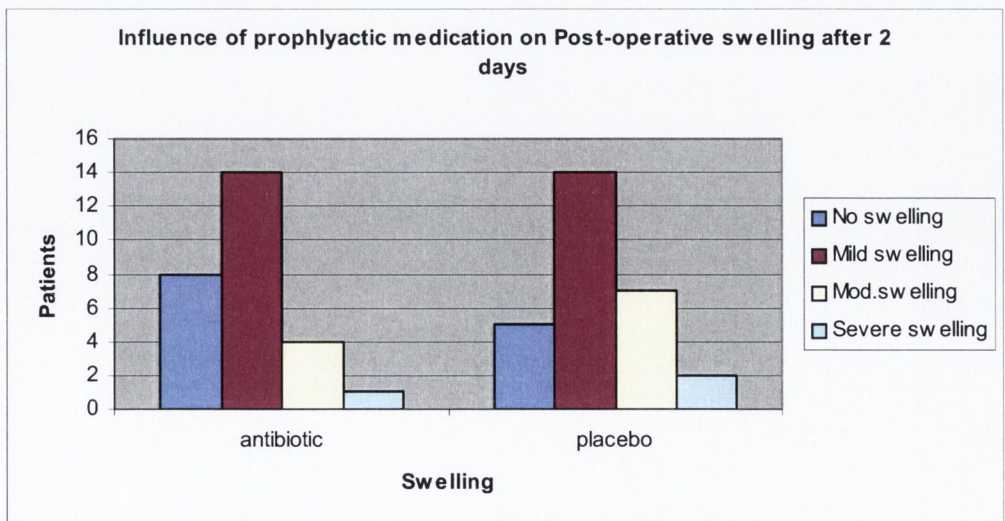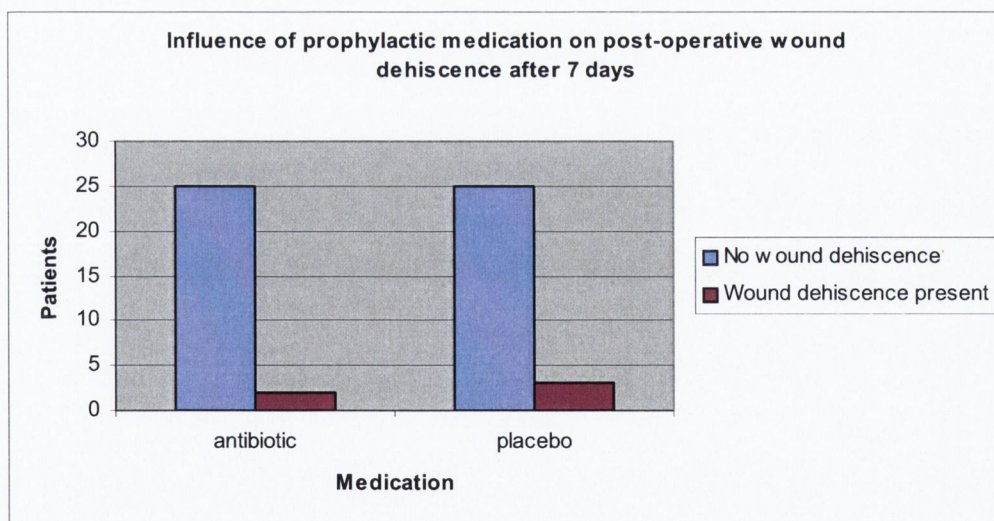

Fig. 4.13 Influence of prophylactic medication on post-operative wound dehiscence after 7 days.

4.4.7 Influence of prophylactic medication on post-operative suppuration after 2 days

Figure 4.14 demonstrates the influence of prophylactic medication on post-operative suppuration after 2 days. The response was similar for both groups.

Medication	Suppuration absent	Suppuration present
Antibiotic	27	0
Placebo	26	2

Table 4.8 **Influence of prophylactic medication on post-operative suppuration after 2 days**
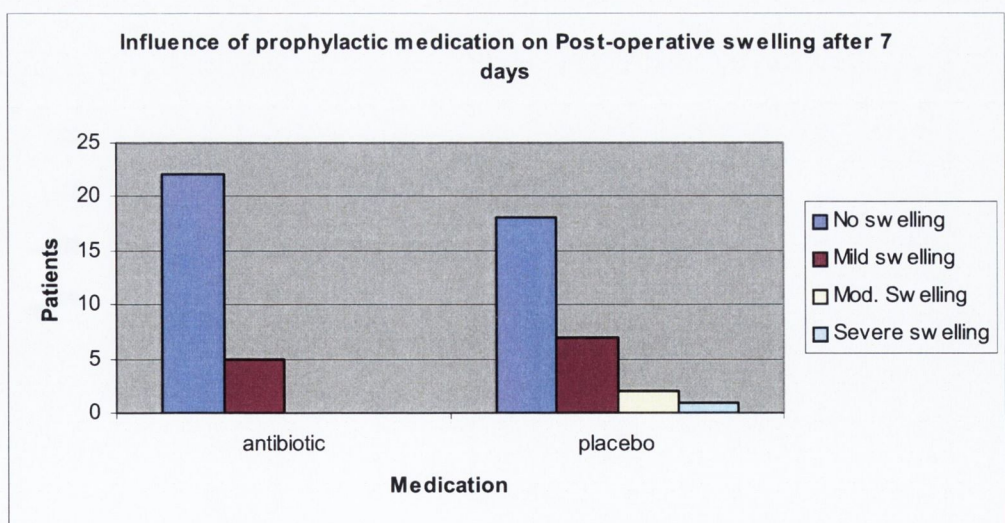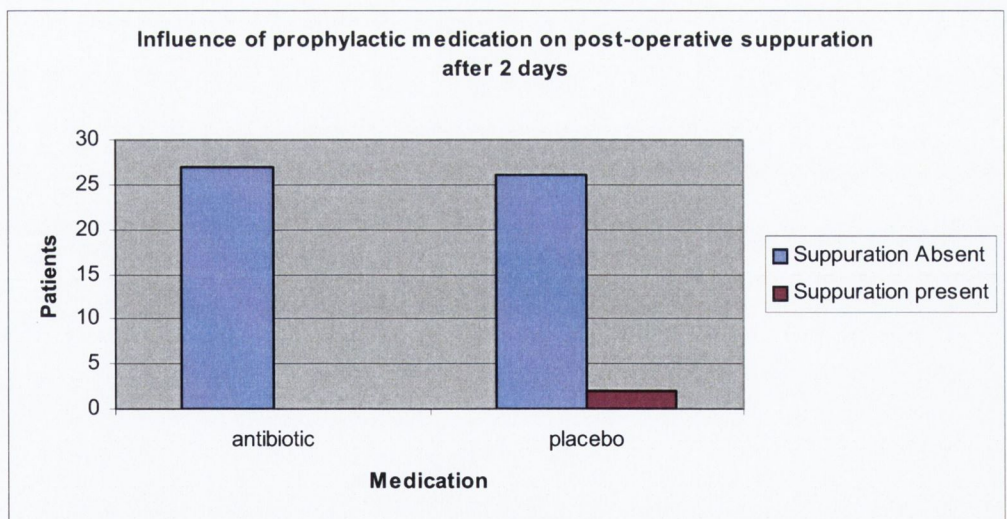

Fig 4.14 **Influence of prophylactic medication on post-operative suppuration after 2 days.**

4.4.8 Influence of prophylactic medication on post-operative suppuration after 7 days

Figure 4.15 demonstrates the influence of prophylactic medication on post-operative suppuration after 7 days. The response was similar for both groups.

Medication	Suppuration absent	Suppuration present
Antibiotic	27	0
Placebo	26	2

Table 4.9 **Influence of prophylactic medication on post-operative suppuration after 7 days**
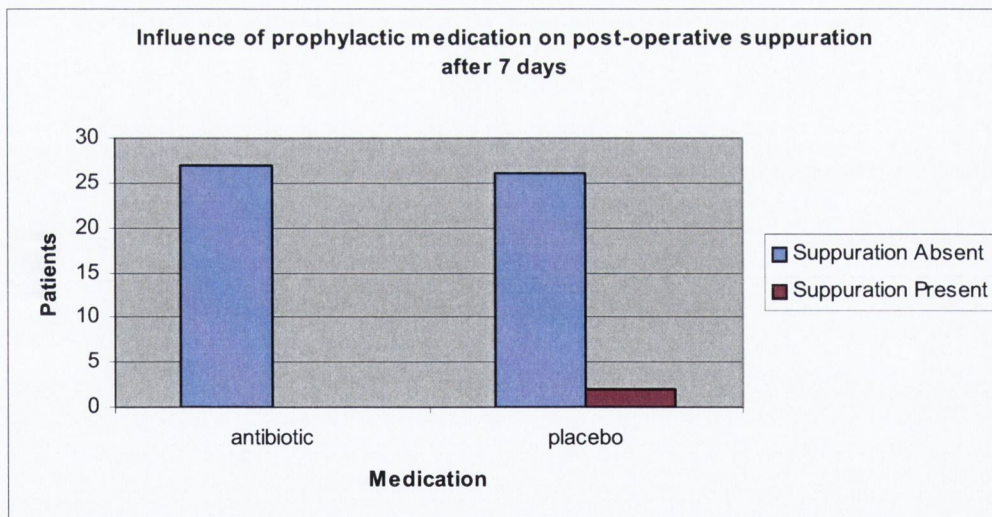
Fig. 4.15 **Influence of prophylactic medication on post-operative suppuration after 7 days.**

4.5 Influence of osseointegration on pain experience

4.5.1 Influence of osseointegration of dental implants on pain experience during surgery

Figure 4.16 demonstrates the influence of osseointegration of dental implants on pain experience during surgery. There was no statistically significant difference observed between the two groups (Wilcoxon p=0.58).
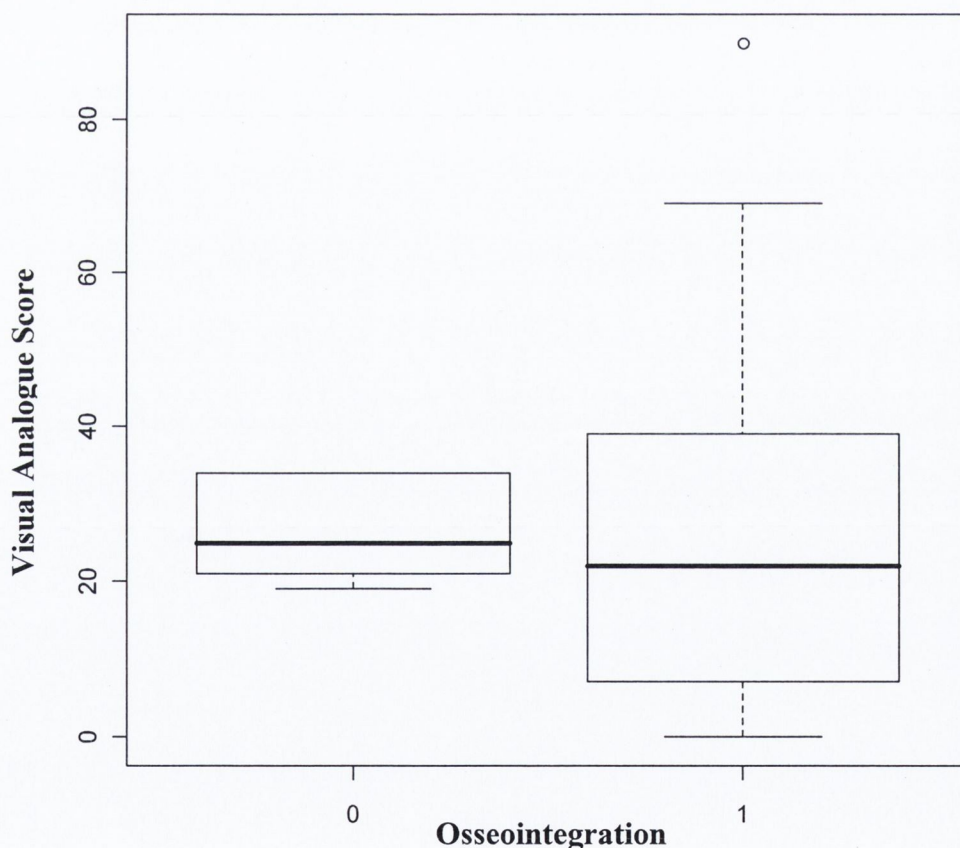
Fig. 4.16 Boxplot comparing the influence of successful osseointegration on pain experience during surgery using visual analogue scores on the Y-axis; 0=failed osseointegration, 1=successful osseointegration.

4.5.2   Influence of osseointegration of dental implants on pain experience after 2 days

Figure 4.17 demonstrates the influence of successful osseointegration of dental implants on pain experience after 2 post-operative days. Patients' whose implants failed to successfully osseointegrate appeared to show higher VAS pain scores (Wilcoxon p=0.003).
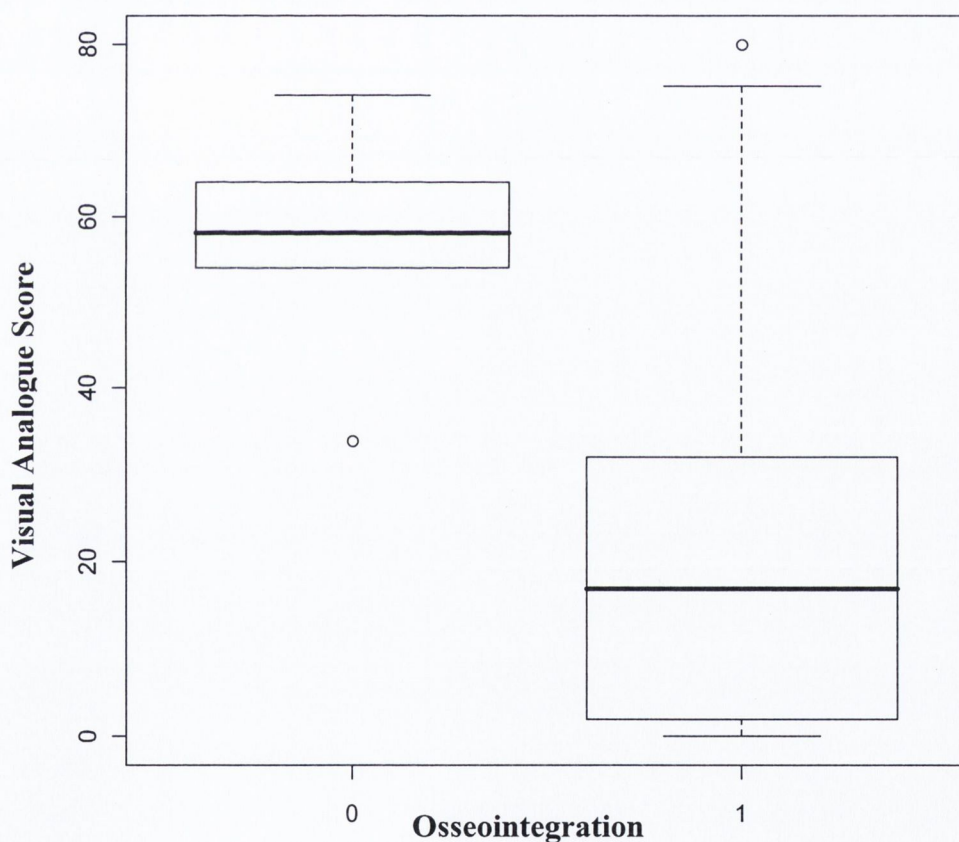
Fig. 4.17   Boxplot comparing the influence of successful osseointegration on pain experience after 2 days using visual analogue scores on the Y-axis; 0=failed osseointegration, 1=successful osseointegration.

4.5.3 Influence of osseointegration of dental implants on pain experience after 7 days

Figure 4.18 demonstrates the influence of successful osseointegration of dental implants on pain experience after 7 post-operative days. Patients' whose implants failed to successfully osseointegrate appeared to show higher VAS pain scores (Wilcoxon p=0.0005).
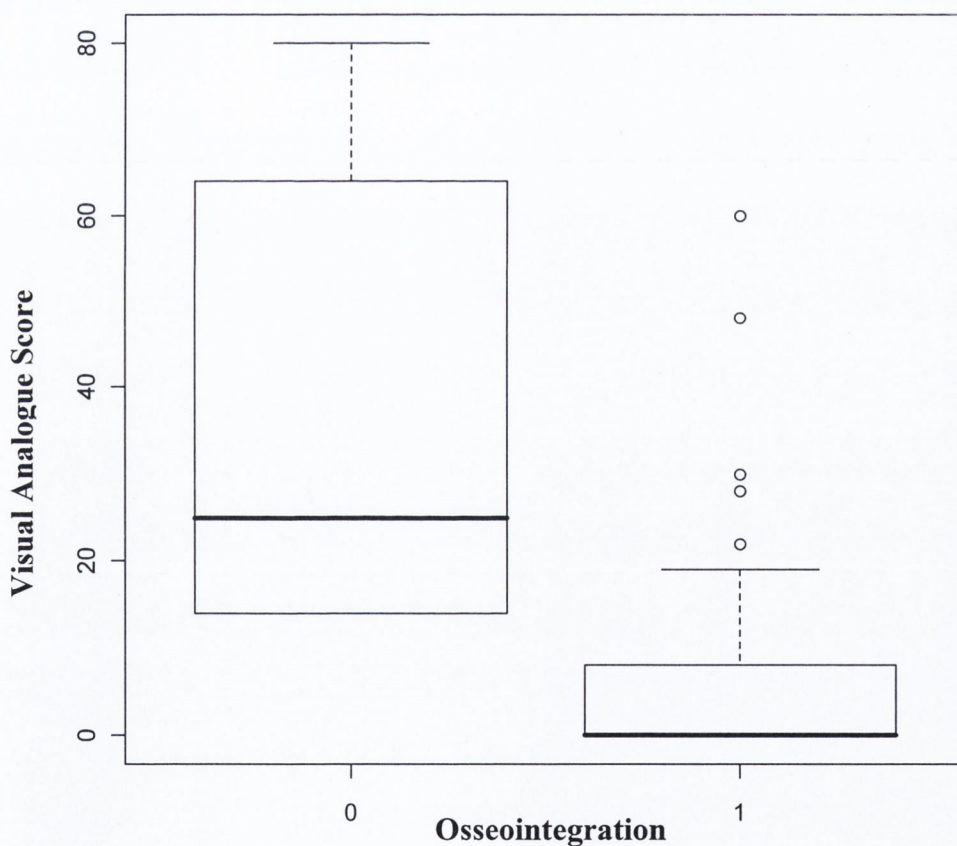
Fig. 4.18 Boxplot comparing the influence of successful osseointegration on pain experience after 7 days using visual analogue scores on the Y-axis; 0=failed osseointegration, 1=successful osseointegration.

4.5.4 Influence of osseointegration of dental implants on pain experience represented by the number of analgesics taken after7 days

Figure 4.19 demonstrates the influence of successful osseointegration of dental implants on pain experience expresed as the number of paracetamol 500mg tablets taken after 7 post-operative days. Patients' whose implants failed to successfully osseointegrate appeared to take more analgesic tablets (Wilcoxon $p=0.001$).
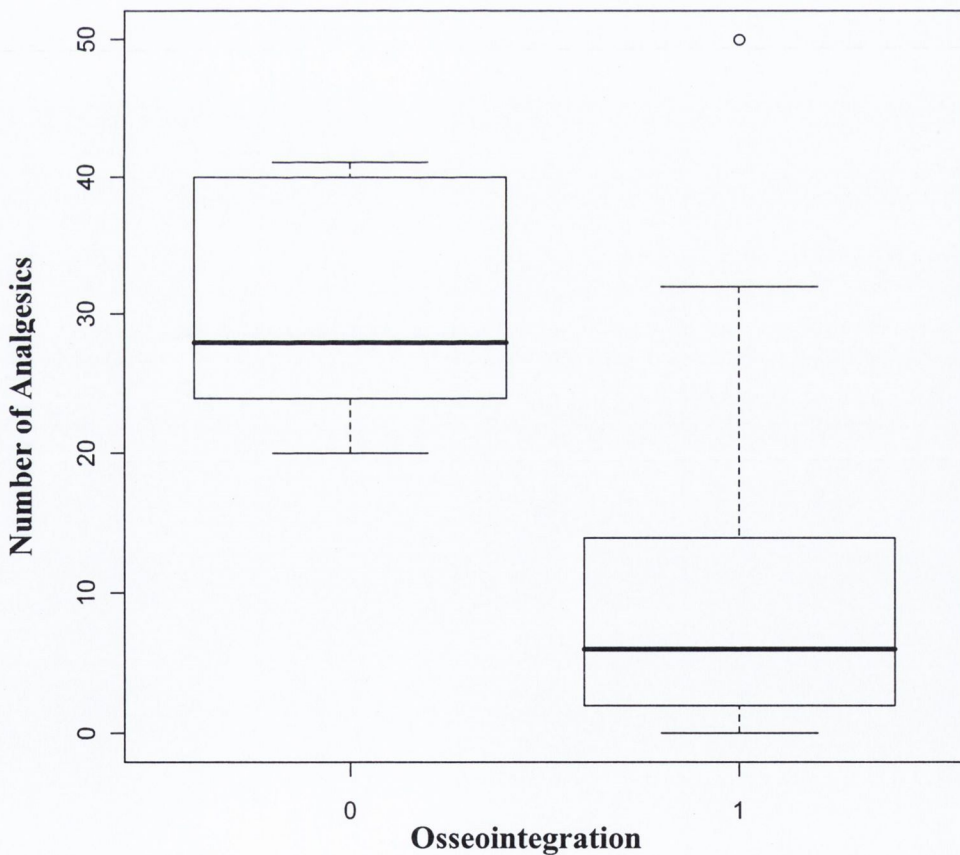
Fig. 4.19 Boxplot comparing the influence of successful osseointegration on pain experience after 7 days represented by the number of analgesics taken on the Y-axis; 0=failed osseointegration, 1=successful osseointegration.

4.6   *Influence of osseointegration on daily activities*

4.6.1   Influence of osseointegration of dental implants on daily activities after 2 days

Figure 4.20 demonstrates the influence of successful osseointegration of dental implants on interference with daily activities after 2 post-operative days. Patients' whose implants failed to successfully osseointegrate appeared to have higher VAS daily activity scores (Wilcoxon $p=0.005$).
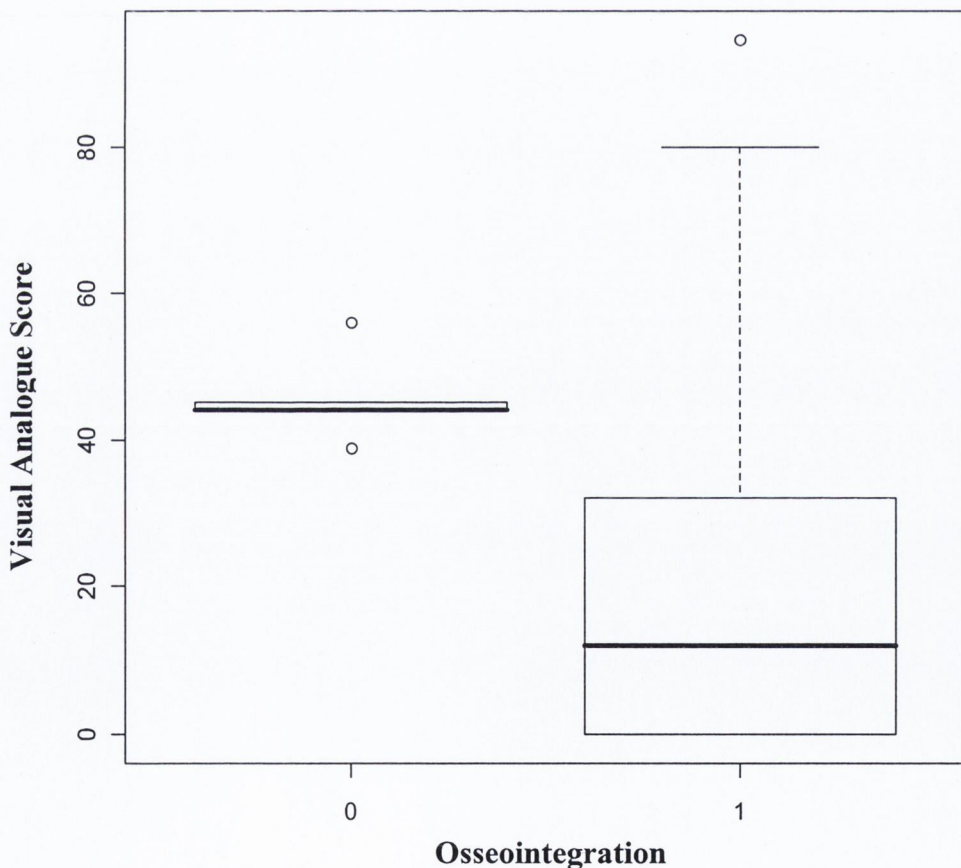
Fig. 4.20   Boxplot comparing the influence of successful osseointegration on daily activities after 2 days using visual analogue scores on the Y-axis; 0=failed osseointegration, 1=successful osseointegration.

4.6.2 Influence of osseointegration of dental implants on daily activities after 7 days

Figure 4.21 demonstrates the influence of successful osseointegration of dental implants on interference with daily activities after 7 post-operative days. Patients' whose implants failed to successfully osseointegrate appeared to show higher VAS daily activity scores, however statistical analysis was not possible due to the nature of the data.
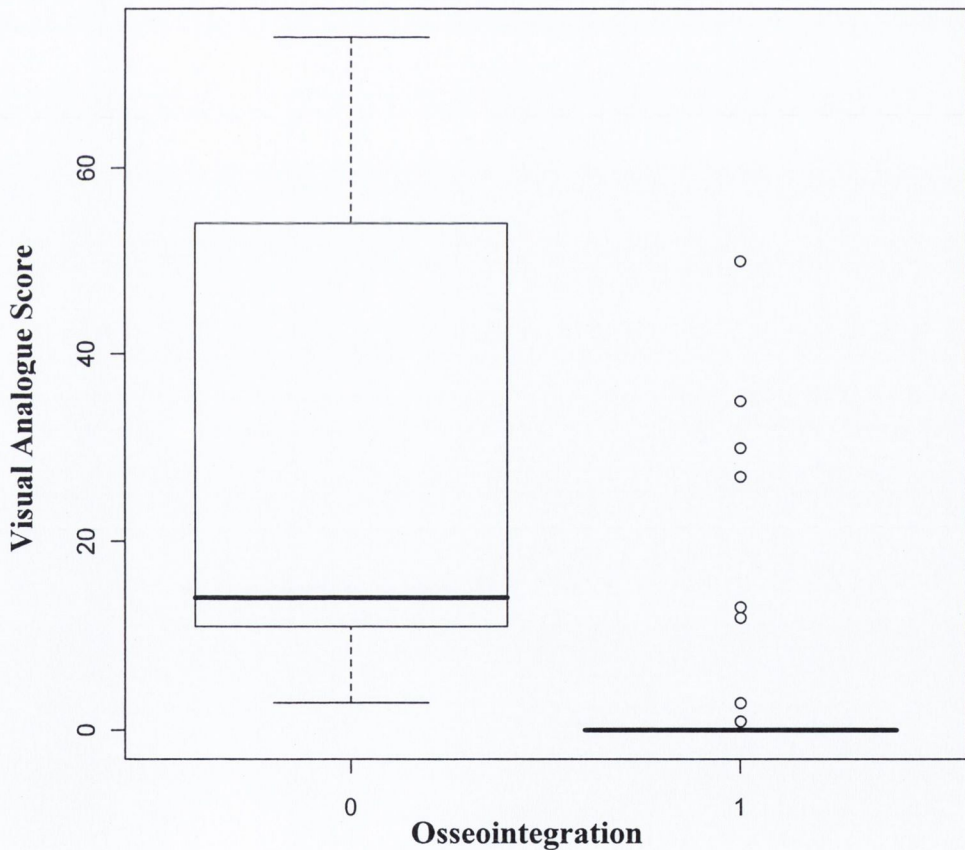
Fig. 4.21 Boxplot comparing the influence of successful osseointegration on daily activities after 7 days using visual analogue scores on the Y-axis; 0=failed osseointegration, 1=successful osseointegration.

4.7   Incision length on pain experience

4.7.1   Influence of incision length on pain experience during surgery

Figure 4.22 demonstrates the influence of incision length on pain experience during surgery. No relationship was observed (Spearman rank correlation r=0.18, p=0.20).
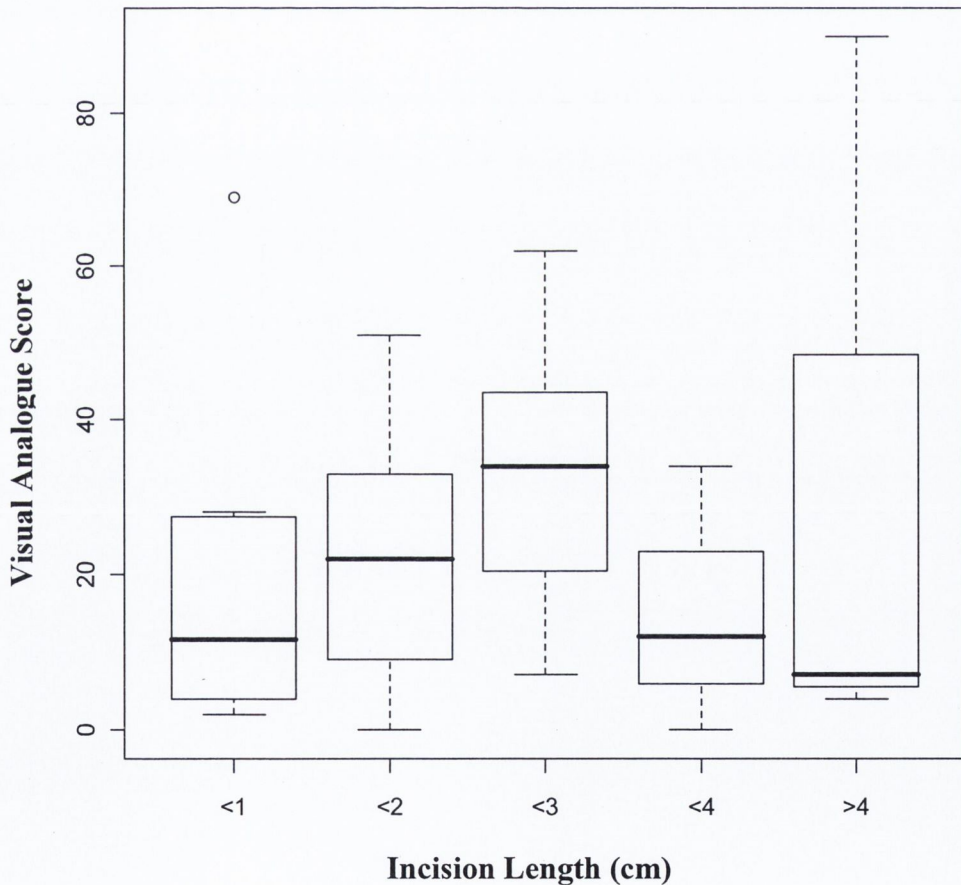
Fig. 4.22   Boxplot comparing the influence of the length of incision (cm, X-axis) on pain experience during surgery using visual analogue scores on the Y=axis.

4.7.2   Influence of incision length on pain experience after 2 days

Figure 4.23 demonstrates the influence of incision length on pain experience after 2 post-operative days. The longer incisions appeared to be related to higher VAS pain scores (Spearman rank correlation r=0.27, p=0.04).
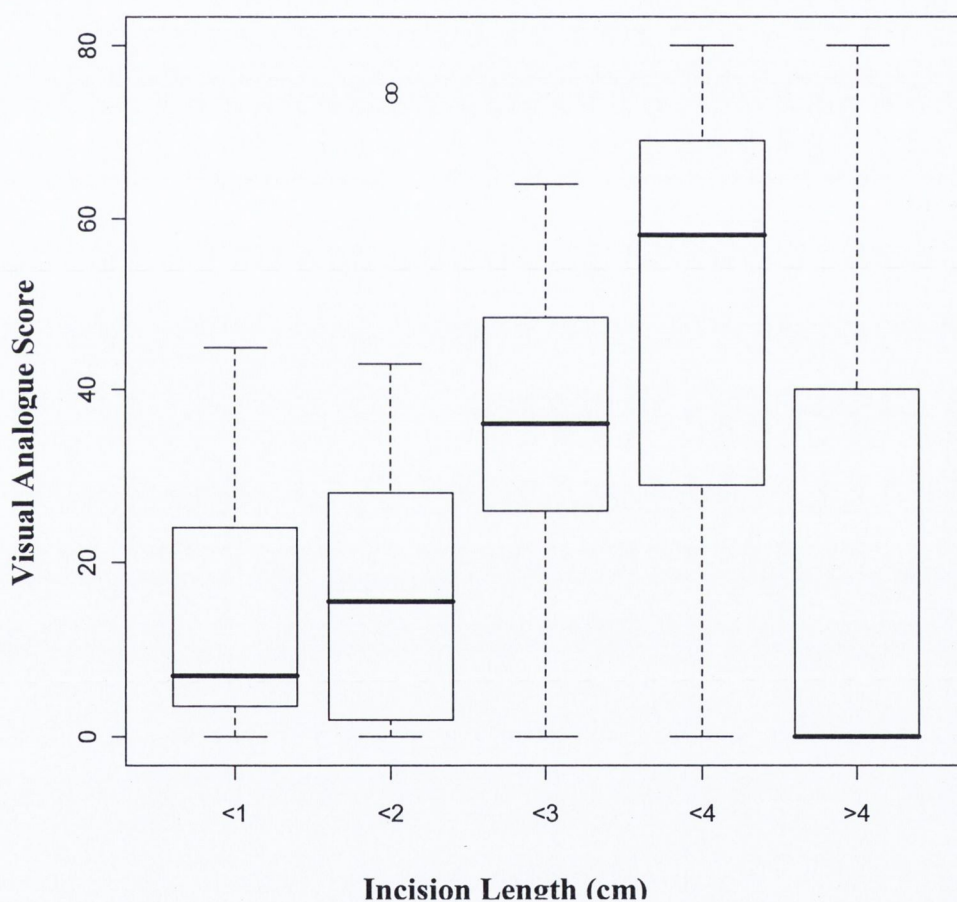
Fig. 4.23   Boxplot comparing the influence of the length of incision (cm, X-axis) on pain experience after 2 days using visual analogue scores on the Y=axis.

4.7.3   Influence of incision length on pain experience after 7 days

Figure 4.24 demonstrates the influence of incision length on pain experience after 7 post-operative days. The longer incisions appeared to be related to higher VAS pain scores (Spearman rank correlation r=0.32, p=0.02).
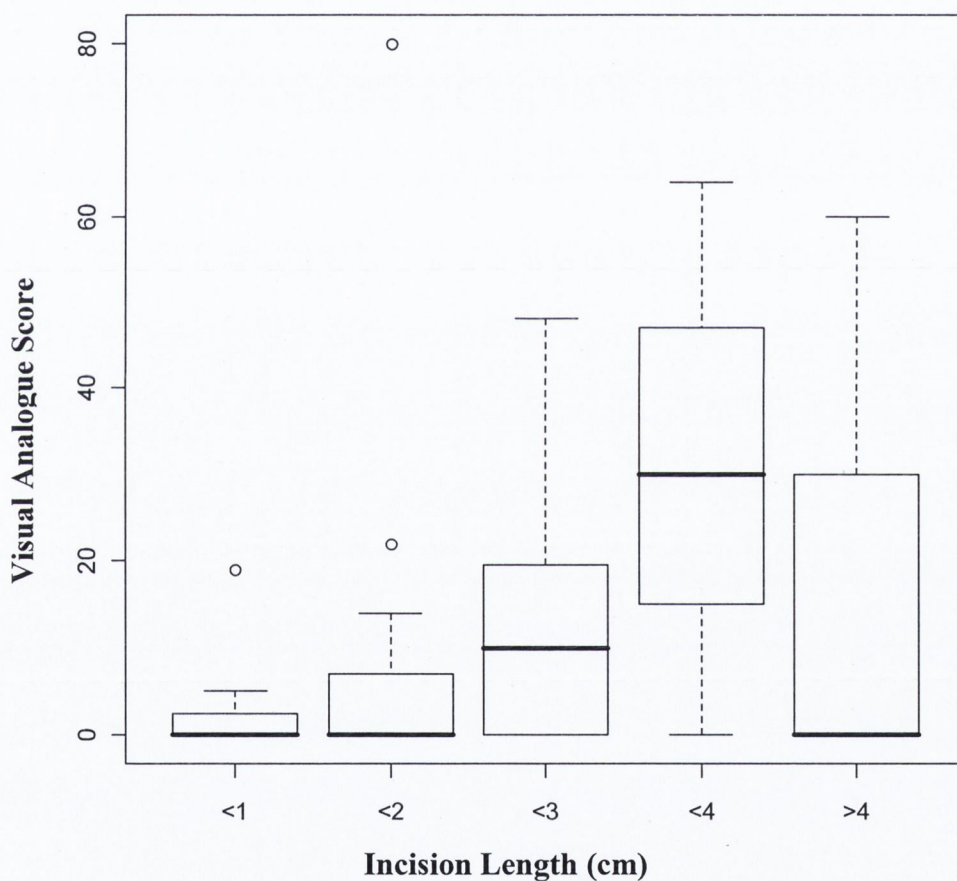
Fig. 4.24   Boxplot comparing the influence of the length of incision (cm, X-axis) on pain experience after 7 days using visual analogue scores on the Y=axis.

4.7.4 Influence of incision length on pain experience represented by the number of analgesics taken after 7 days

Figure 4.25 demonstrates the influence of incision length on pain experience represented by the number of paracetamol 500mg tablets taken after 7 post-operative days. The longer incisions appeared to be related to higher numbers of analgesic tablets taken (Spearman rank correlation r=0.41, p=0.002).
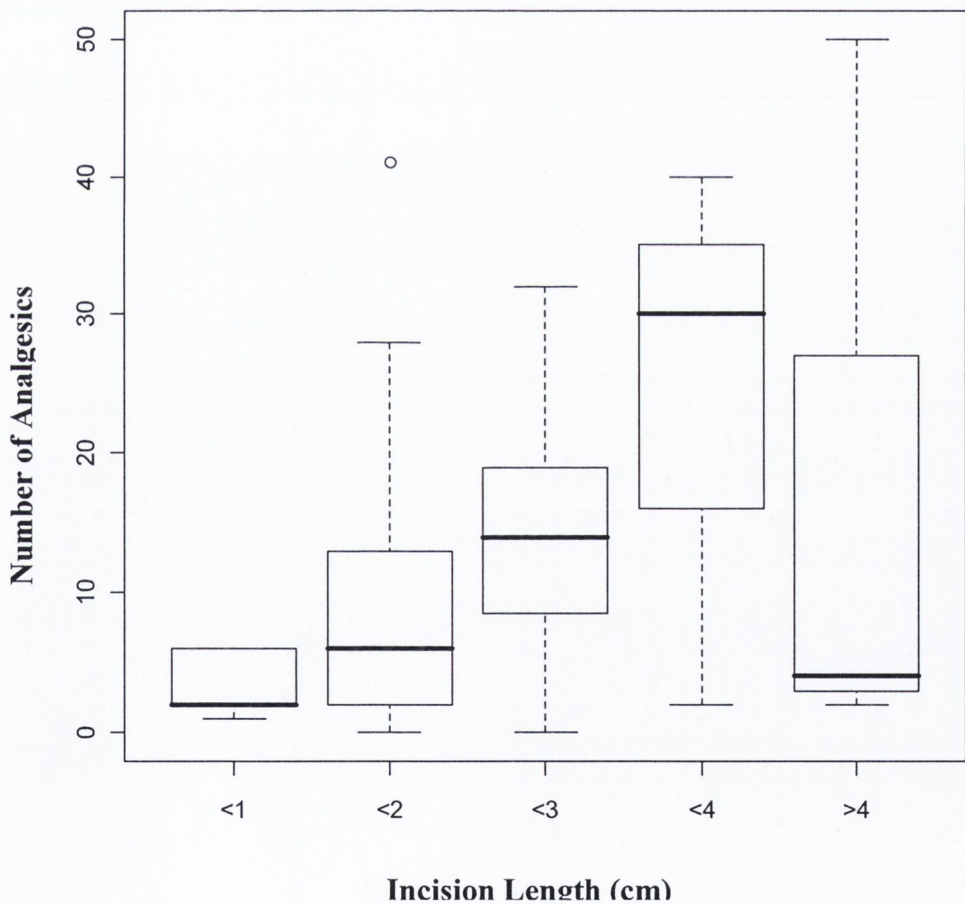
Fig. 4.25 **Boxplot comparing the influence of the length of incision (cm, X-axis) on pain experience after 7 days represented by the number of analgesics taken on the Y=axis.**

4.8 Incision length on daily activities

4.8.1   Influence of incision length on daily activities after 2 days

Figure 4.26 demonstrates the influence of incision length on interference with daily activities after 2 post-operative days. The longer incisions appeared to be related to higher VAS activity scores (Spearman rank correlation r=0.31, p=0.02).
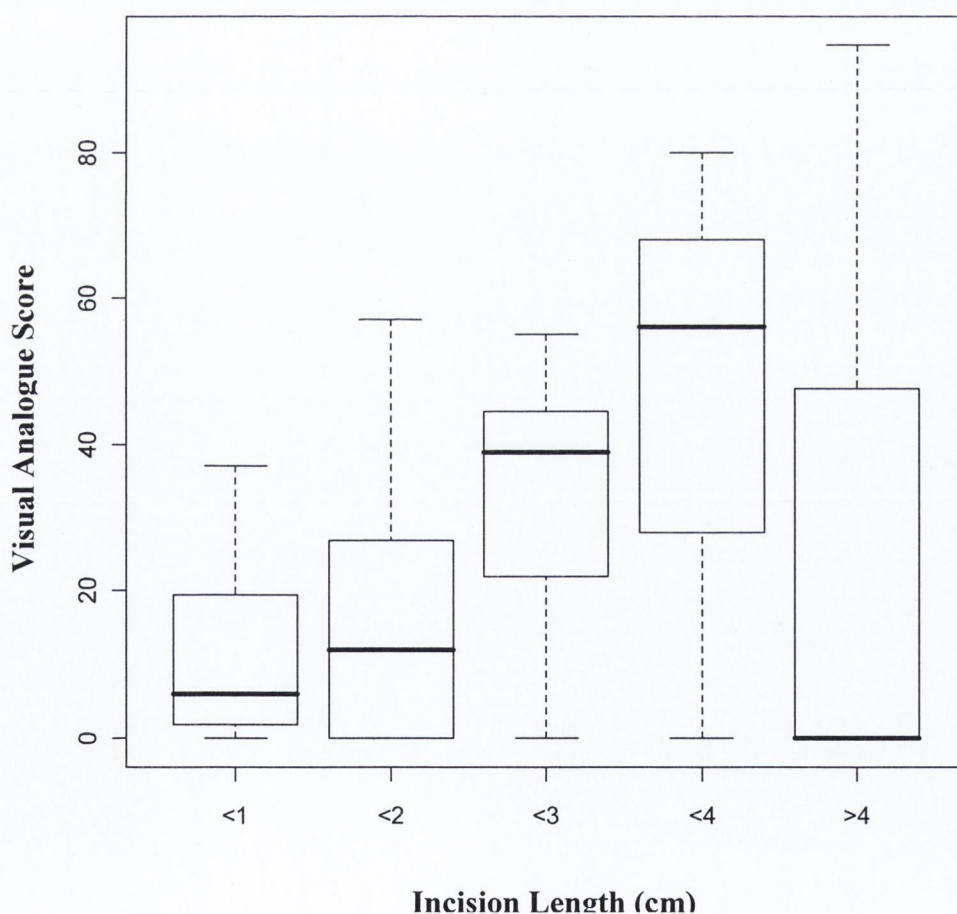
Fig. 4.26   Boxplot comparing the influence of the length of incision (cm, X-axis) on daily activities after 2 days using visual analogue scores on the Y=axis.

4.8.2 Influence of incision length on daily activities after 7 days

Figure 4.27 demonstrates the influence of incision length on interference with daily activities after 7 post-operative days. The longer incisions appeared to be related to higher VAS activity scores (Spearman rank correlation r=0.33, p=0.01).
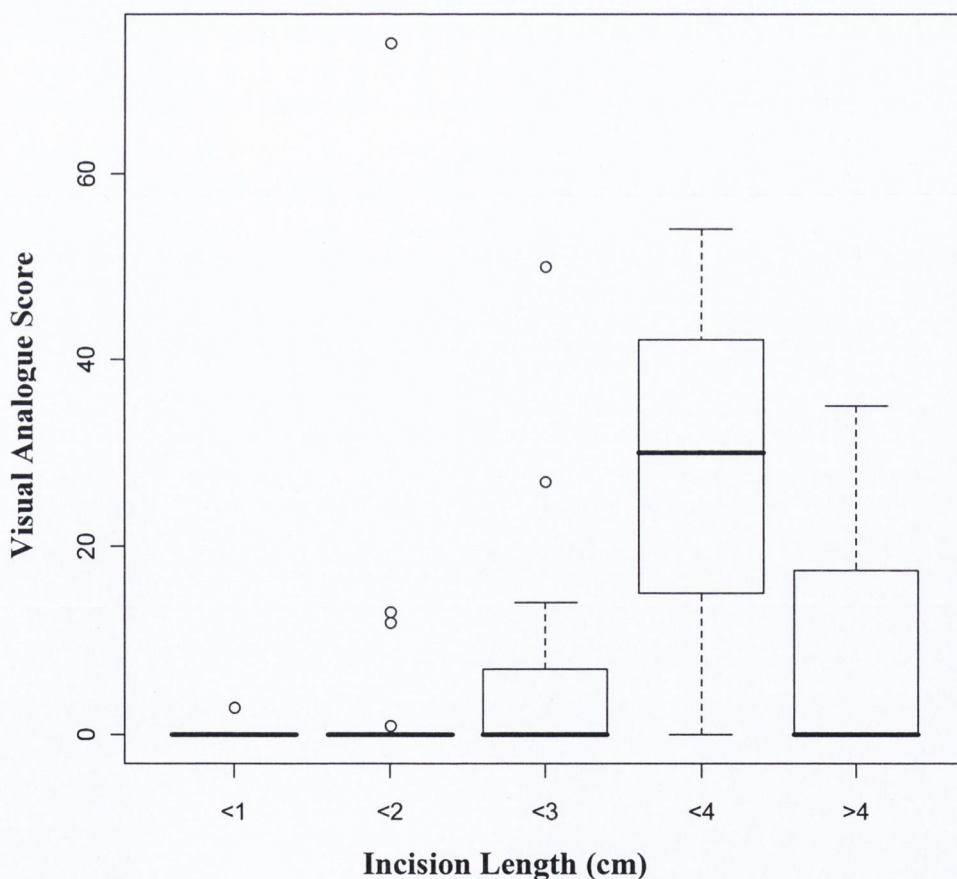
Fig. 4.27 **Boxplot comparing the influence of the length of incision (cm, X-axis) on daily activities after 7 days using visual analogue scores on the Y=axis.**

4.9 Duration of surgery on pain experience

4.9.1 Influence of duration of surgery on pain experience during surgery

Figure 4.28 demonstrates the influence of duration of surgery on pain experience during surgery. No relationship was observed (Spearman rank correlation r=-0.003, p=0.98).

Fig. 4.28 **Influence of duration of surgery on pain experience during surgery using visual analogue scores on the Y=axis and minutes on the X-axis.**

4.9.2   Influence of duration of surgery on pain experience after 2 days

Figure 4.29 demonstrates the influence of duration of surgery on post-operative pain experience after 2 days. Longer surgery time appeared to be related to higher VAS pain scores (Spearman rank correlation r=0.34, p=0.01).
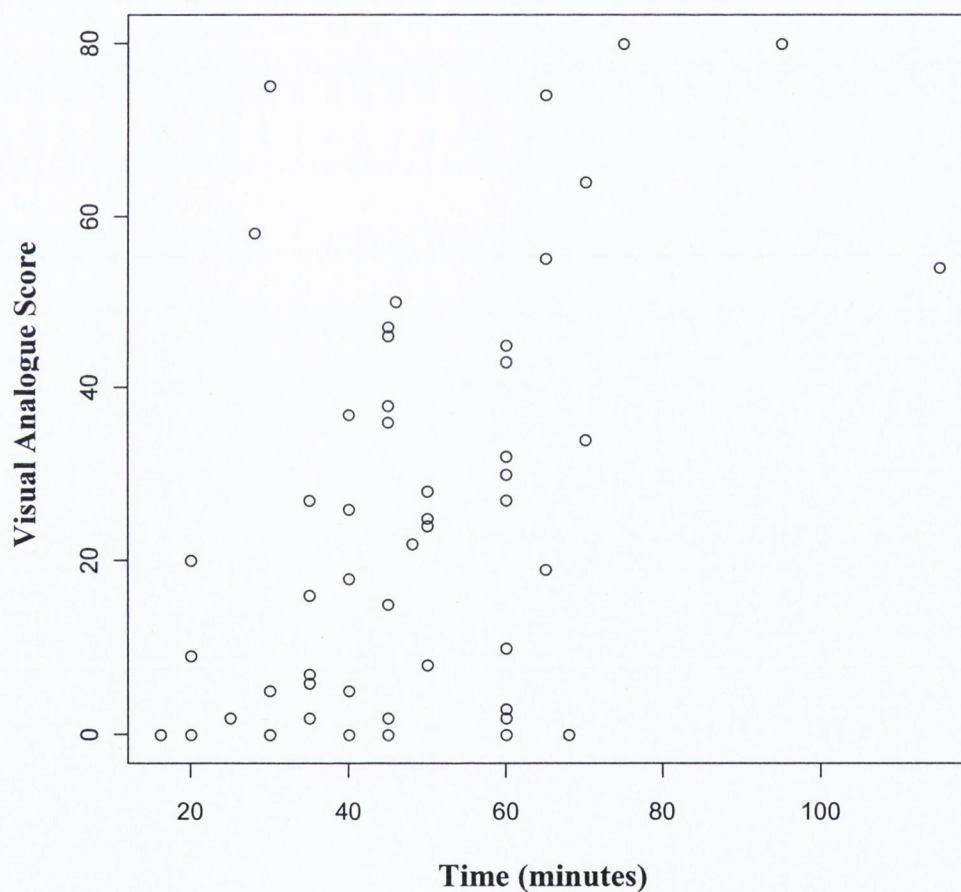
Fig. 4.29   **Influence of duration of surgery on pain experience after 2 days using visual analogue scores on the Y=axis, and minutes on the X-axis.**

4.9.3 Influence of duration of surgery on pain experience after 7 days

Figure 4.30 demonstrates the influence of duration of surgery on post-operative pain experience after 7 days. No statistically significant difference was observed (Spearman rank correlation r=0.21, p=0.13).
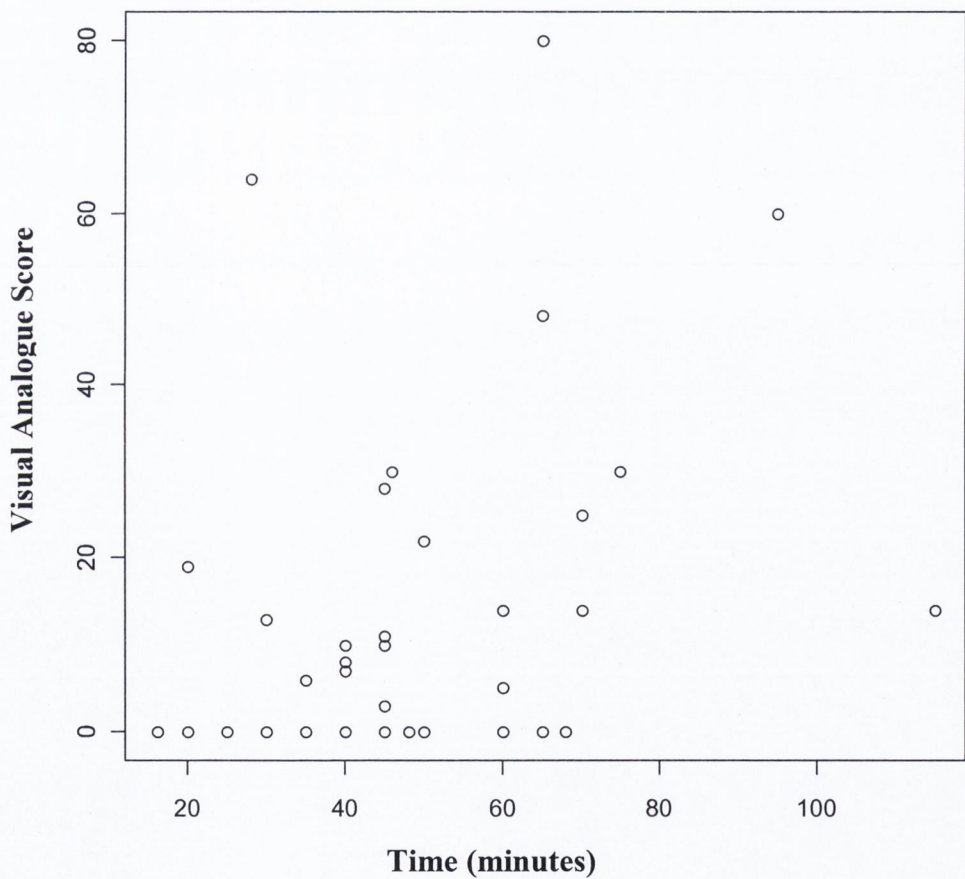
Fig. 4.30 Influence of duration of surgery on pain experience after 7 days using visual analogue scores on the Y=axis, and minutes on the X-axis.

4.9.4   Influence of duration of surgery on pain experience represented by the number of analgesics taken after 7 days

Figure 4.31 demonstrates the influence of duration of surgery on post-operative pain experience after represented by the number of paracetamol 500mg tablets taken 7 days. Longer surgery time appeared to be related to a higher number of analgesic tablets taken (Spearman rank correlation r=0.31, p=0.02).
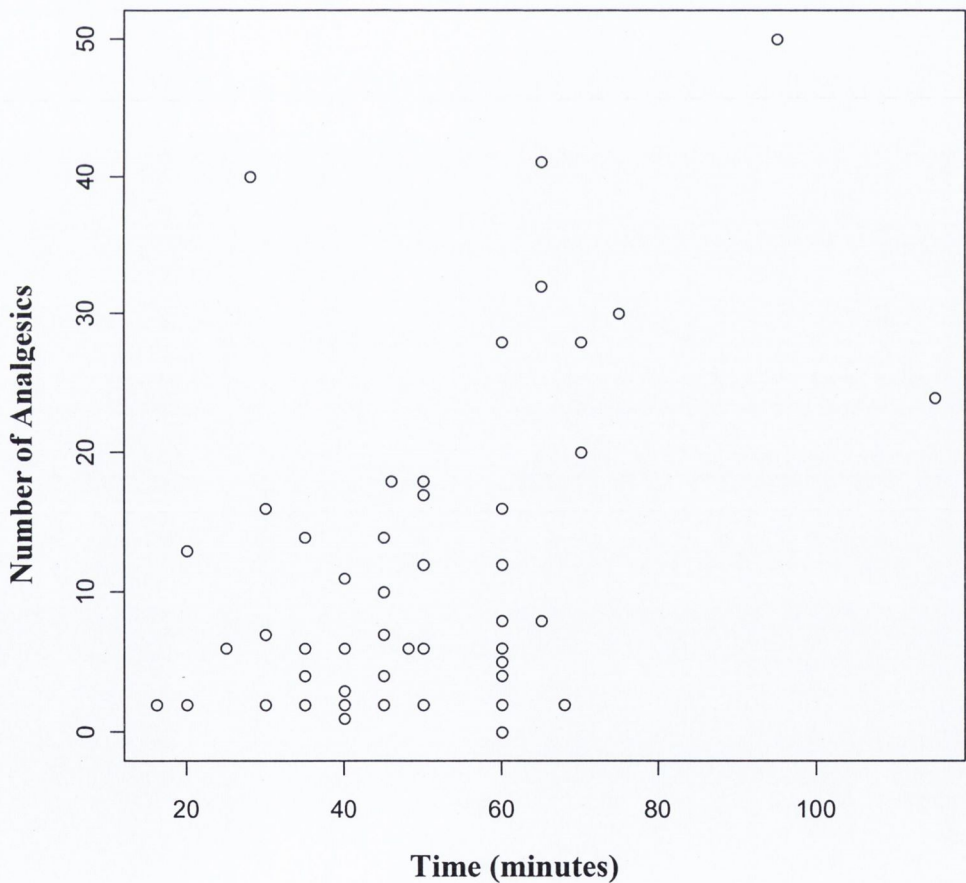
Fig. 4.31   Influence of duration of surgery on pain experience after 7 days represented by the number of analgesics taken on the Y=axis, and minutes on the X-axis.

4.10 *Duration of surgery on daily activities*

4.10.1 Influence of duration of surgery on daily activities after 2 days

Figure 4.32 demonstrates the influence of duration of surgery on daily activities after 2 days. Longer surgery time appeared to be related to higher VAS activity scores (Spearman rank correlation r=0.30, p=0.02).
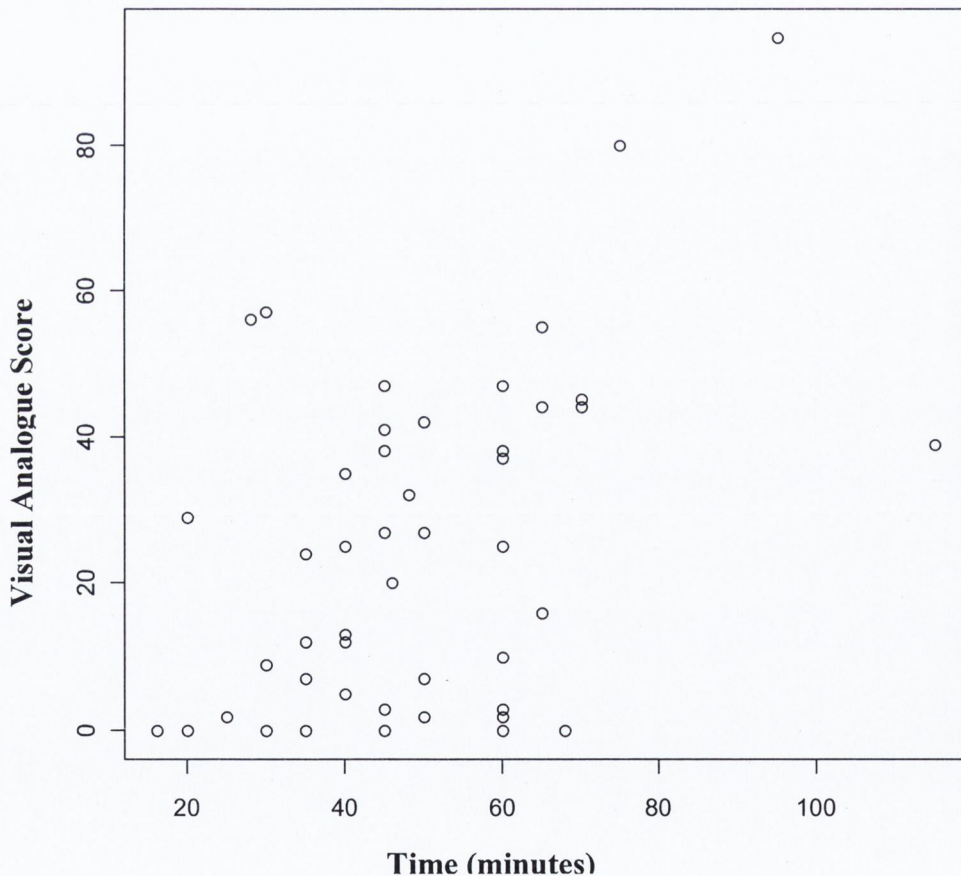
Fig. 4.32 **Influence of duration of surgery on daily activities after 2 days using visual analogue scores on the Y=axis, and minutes on the X-axis.**

4.10.2   Influence of duration of surgery on daily activities after 7 days

Figure 4.33 demonstrates the influence of duration of surgery on daily activities after 7 days. Longer surgery time appeared to be related to higher VAS activity scores (Spearman rank correlation r=0.37, p=0.005).
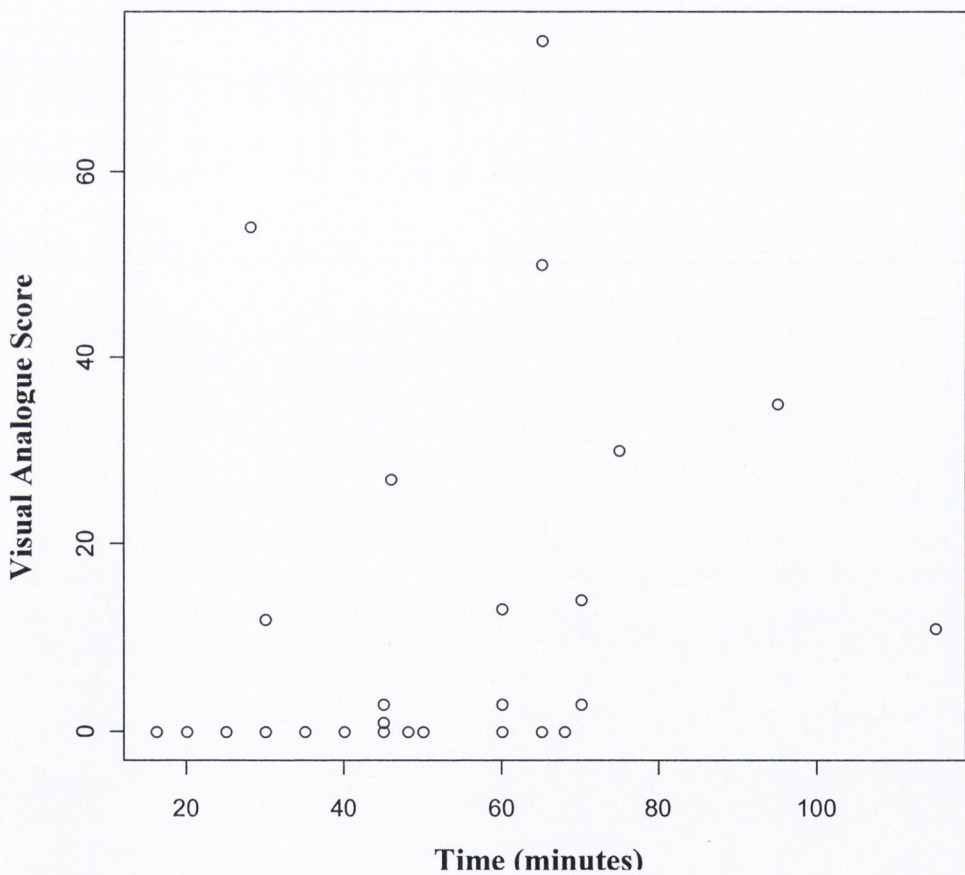
Fig. 4.33   **Influence of duration of surgery on daily activities after 7 days using visual analogue scores on the Y=axis, and minutes on the X-axis.**

4.11 Duration of surgery on post-operative morbidity

4.11.1 Influence of duration of surgery on post-operative swelling after 2 days.

Figure 4.34 demonstrates the influence of duration of surgery on post-operative swelling after 2 days. No statistically significant differences were observed (Kruskal-Wallis p=0.49).
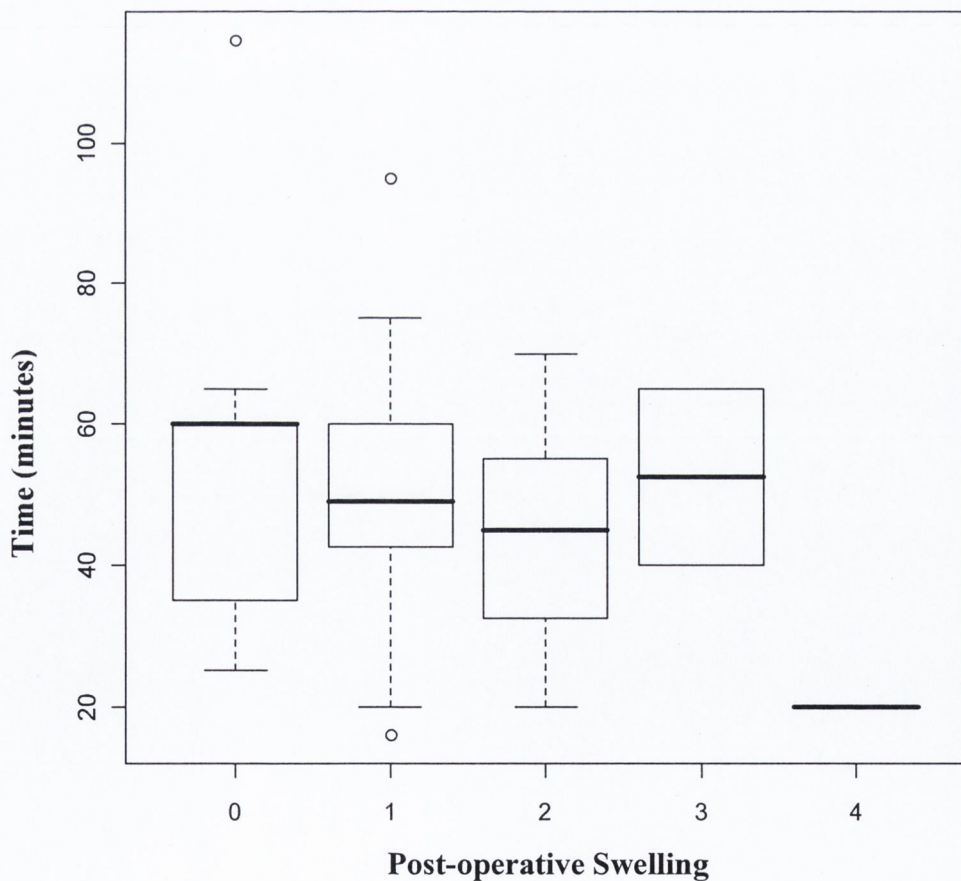
Fig. 4.34 **Influence of duration of surgery on post-operative swelling after 2 days, swelling on the X=axis, and minutes on the Y-axis.**

4.11.2 Influence of duration of surgery on post-operative swelling after 7 days

Figure 4.35 demonstrates the influence of duration of surgery on post-operative swelling after 2 days. No statistically significant differences were observed (Kruskal-Wallis p=0.49).
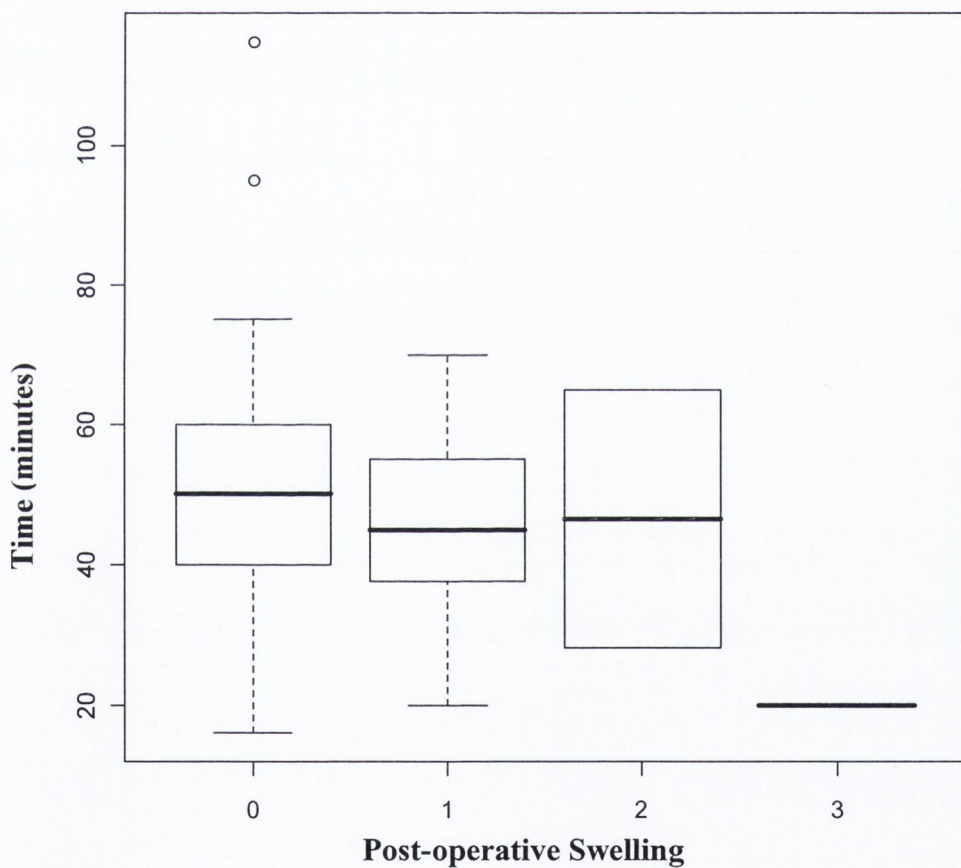
Fig. 4.35 **Influence of duration of surgery on post-operative swelling after 7 days, swelling on the X=axis, and minutes on the Y-axis.**

4.11.3 Influence of duration of surgery on post-operative bruising after 2 days

Figure 4.36 demonstrates the influence of duration of surgery on post-operative bruising after 2 days. Longer surgery time appeared to be related to increased post-operative bruising after 2 days (Wilcoxon p=0.01).
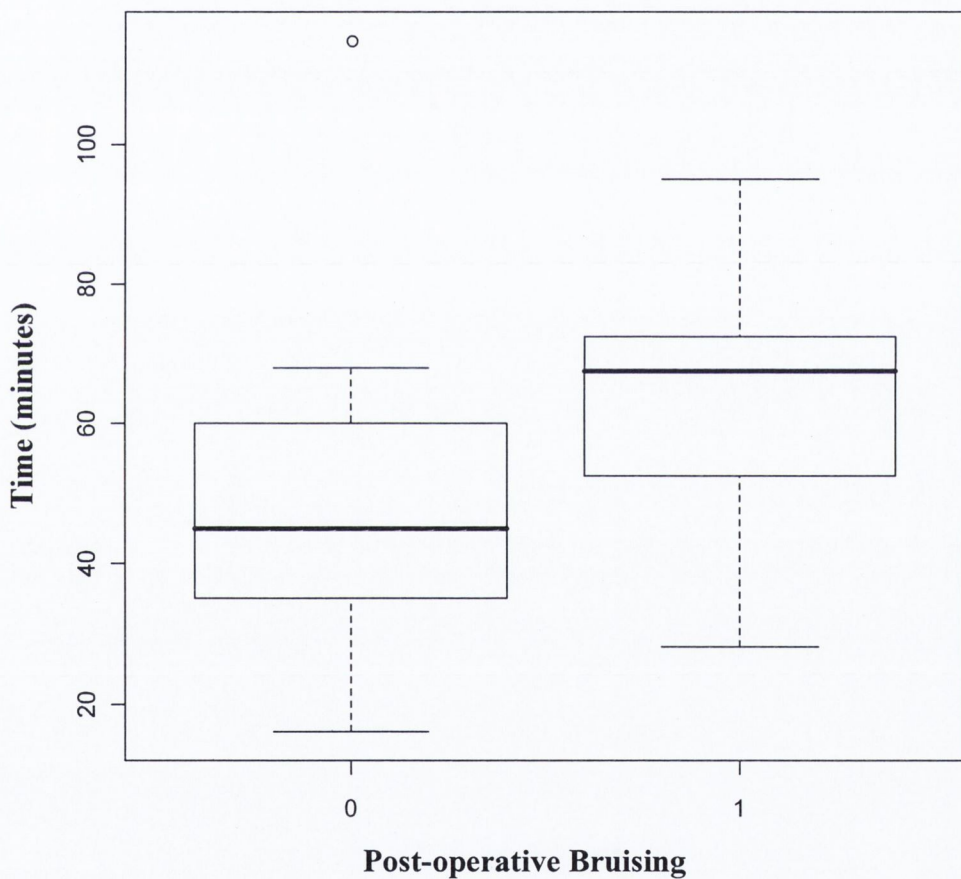
Fig. 4.36 **Influence of duration of surgery on post-operative bruising after 2 days, bruising on the X=axis, and minutes on the Y-axis.**

4.11.4 Influence of duration of surgery on post-operative bruising after 7 days

Figure 4.37 demonstrates the influence of duration of surgery on post-operative bruising after 7 days. No statistically significant differences were observed (Wilcoxon p=0.22).
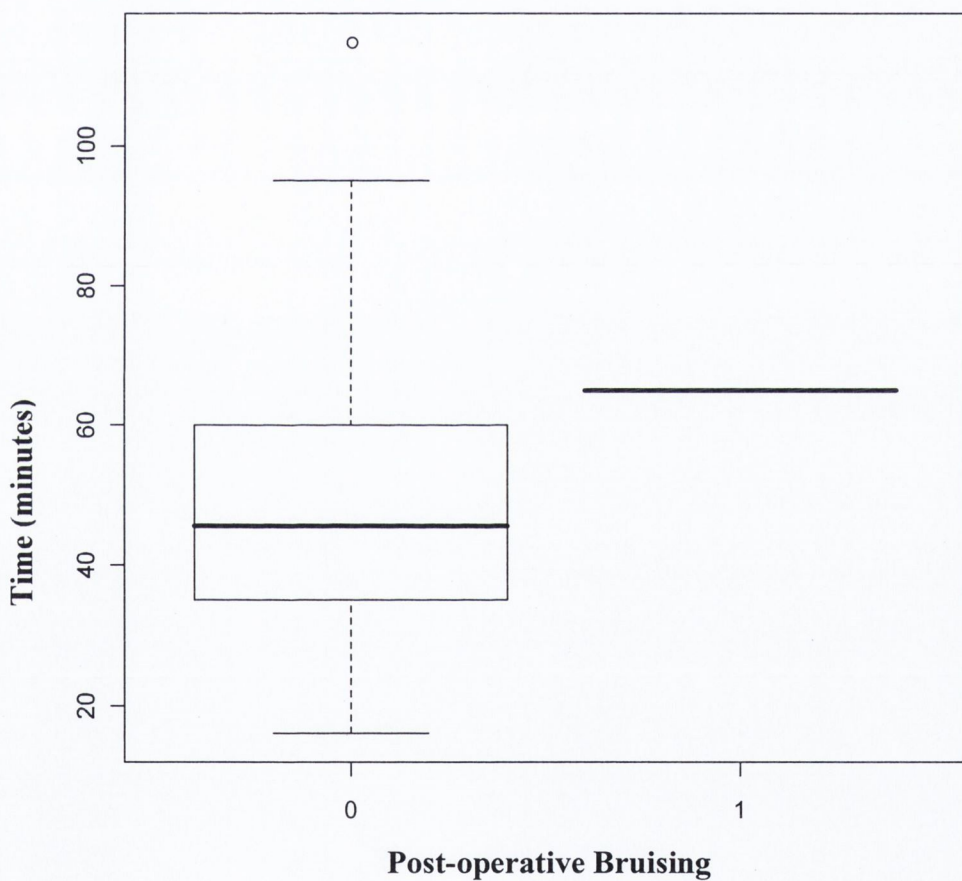
Fig. 4.37 **Influence of duration of surgery on post-operative bruising after 7 days, bruising on the X=axis, and minutes on the Y-axis.**

4.11.5   **Influence of duration of surgery on post-operative wound dehiscence after 2 days**

Figure 4.38 demonstrates the influence of duration of surgery on post-operative wound dehiscence after 2 days. No statistically significant differences were observed (Wilcoxon *p*=0.84).
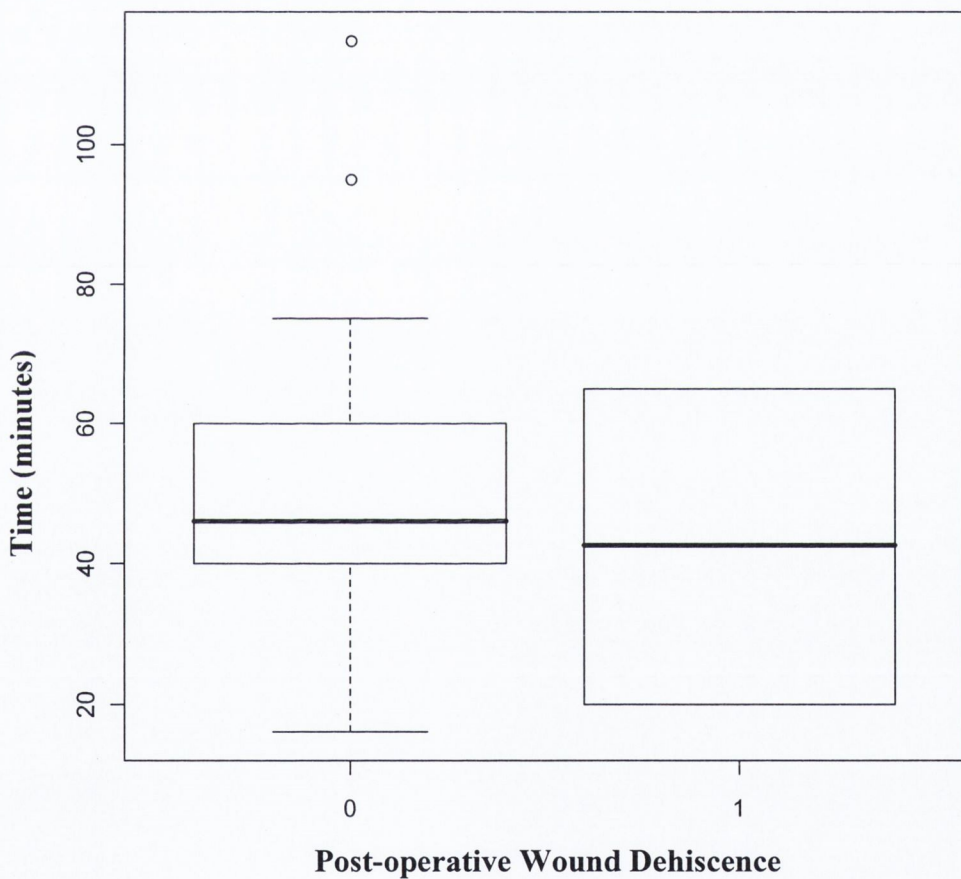
Fig. 4.38   **Influence of duration of surgery on post-operative wound dehiscence after 2 days, wound dehiscence on the X=axis, and minutes on the Y-axis.**

4.11.6 Influence of duration of surgery on post-operative wound dehiscence after 7 days

Figure 4.39 demonstrates the influence of duration of surgery on post-operative wound dehiscence after 7 days. No statistically significant differences were observed (Wilcoxon p=0.32).
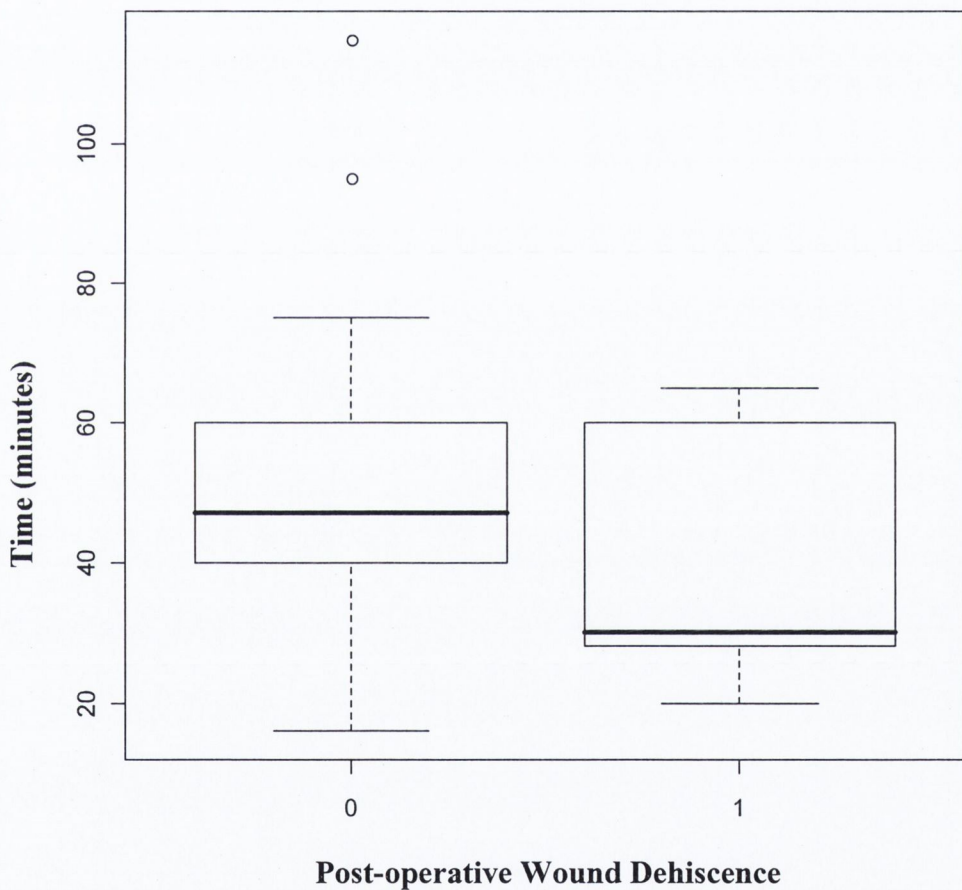
Fig. 4.39   **Influence of duration of surgery on post-operative wound dehiscence after 7 days, wound dehiscence on the X=axis, and minutes on the Y-axis.**

4.11.7   Influence of duration of surgery on post-operative suppuration after 2 days

Figure 4.40 demonstrates the influence of duration of surgery on post-operative suppuration after 2 days. No statistically significant differences were observed (Wilcoxon p=0.95).
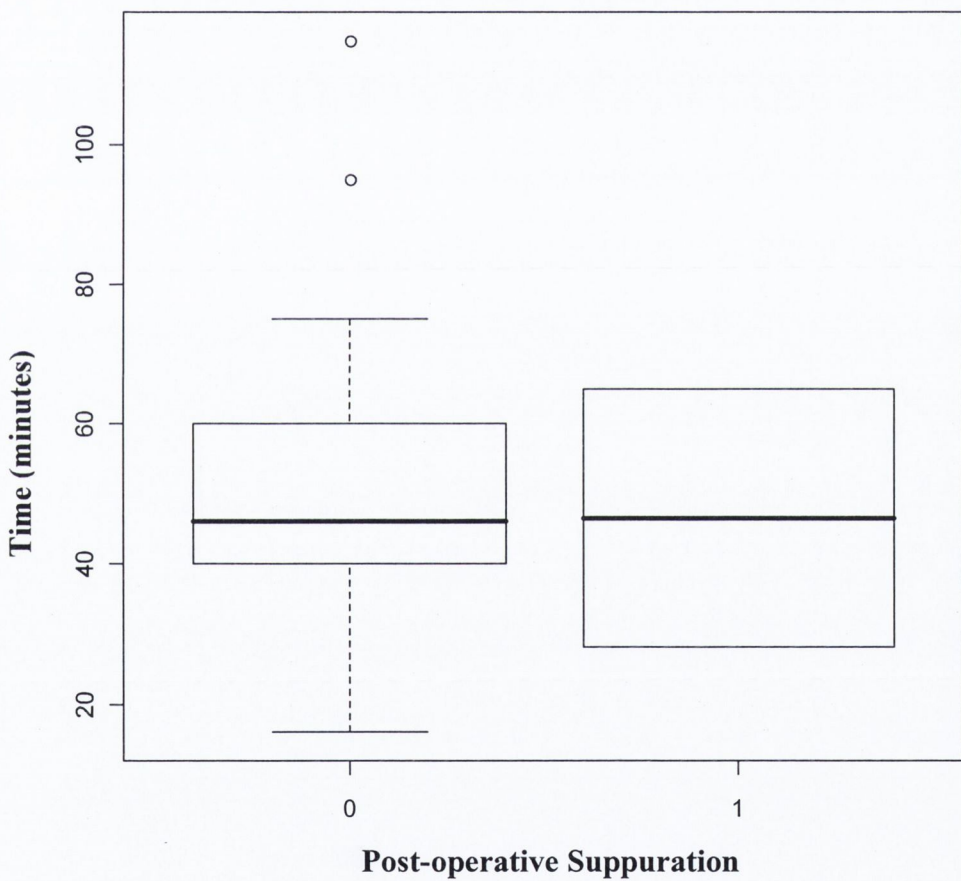
Fig. 4.40   Influence of duration of surgery on post-operative suppuration after 2 days, suppuration on the X=axis, and minutes on the Y-axis.

4.11.8 Influence of duration of surgery on post-operative suppuration after 7 days

Figure 4.41 demonstrates the influence of duration of surgery on post-operative suppuration after 7 days. No statistically significant differences were observed, (Wilcoxon $p=0.95$).
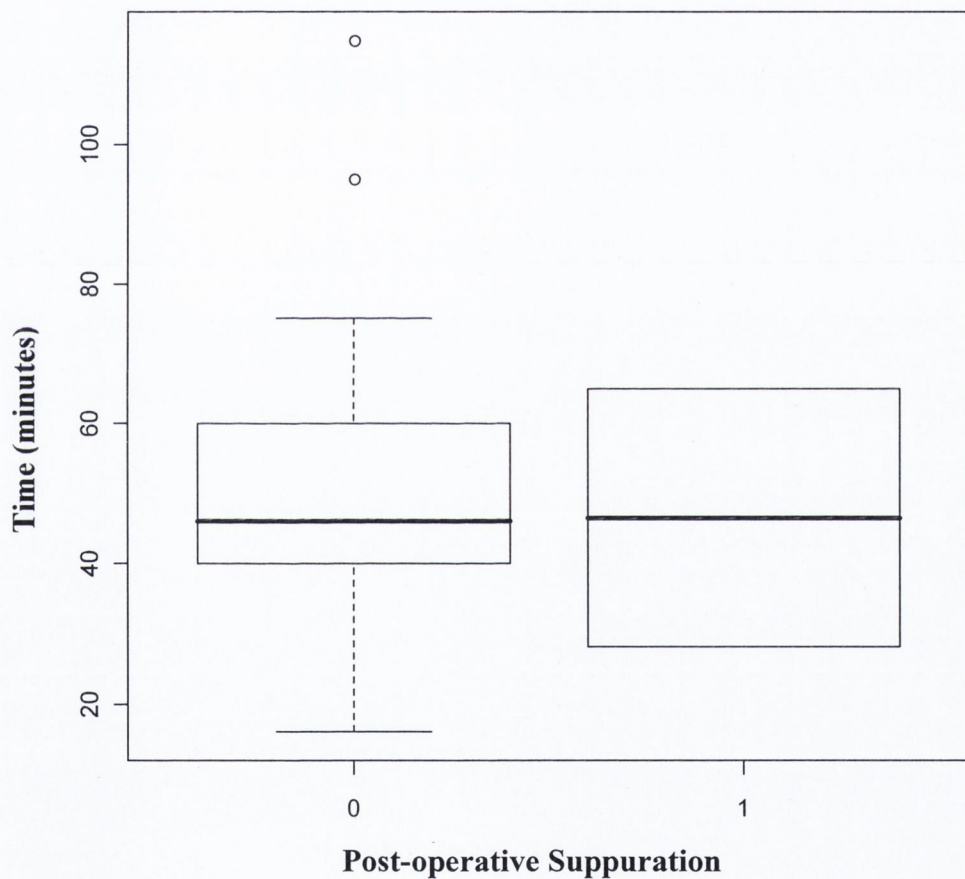
Fig. 4.41 Influence of duration of surgery on post-operative suppuration after 7 days, suppuration on the X=axis, and minutes on the Y-axis.

4.12 Implant System on Osseointegration

Figure 4.42 demonstrates the influence of implant system used on osseointegration of dental implants. No statistically significant differences were observed.

	Oseointegration +ve	Osseointegration -ve
Biomet 3i™	36	4
Brånemark®	7	1
Ankylos®	2	0
Straumann®	5	0

Table 4.10   Influence of implant system on osseointegration of implants
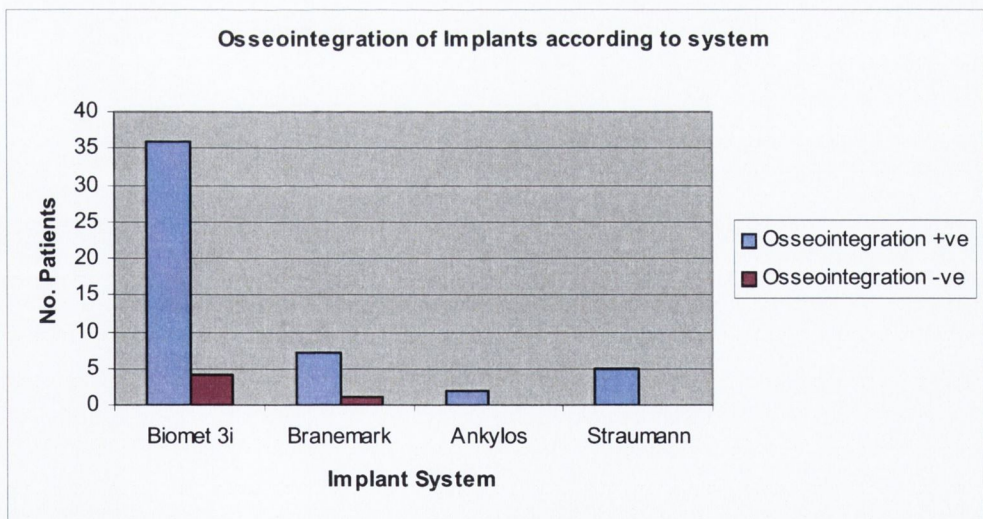
Fig 4.42   Influence of implant system on osseointegration of implants.

4.13 *Number of Implants placed on Osseointegration*

Figure 4.43 demonstrates the influence of number of implants placed on osseointegration of dental implants. Higher number of implants placed appeared to be related higher failure of osseointegration (Fisher's Exact $p=0.01$).

Number of Implants	Osseointegration +ve	Osseointegration -ve
1	32	0
2	15	4
3	3	1

Table 4.11   Influence of number of implants placed on osseointegration of implants
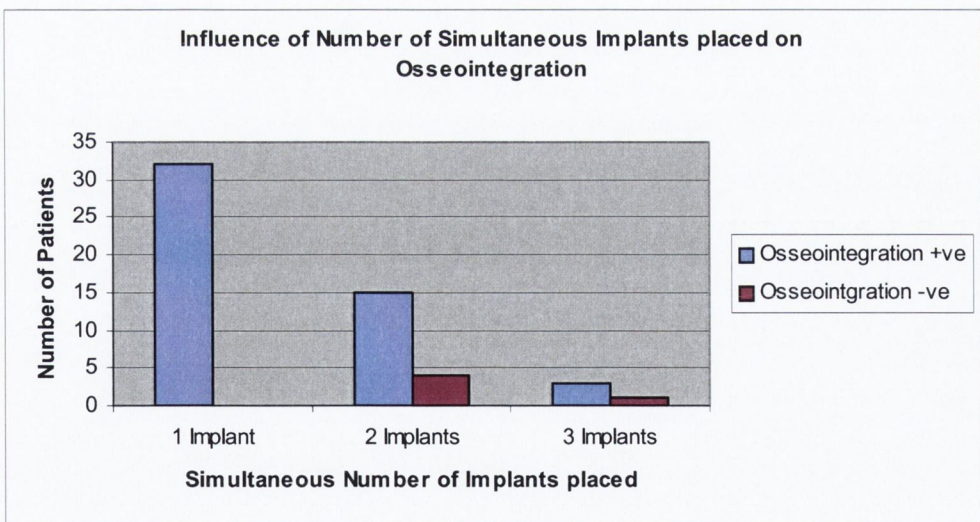
Fig. 4.43   Influence of number of implants placed on osseointegration of implants.

4.14 Duration of Surgery on Osseointegration

Figure 4.44 demonstrates the influence of duration of surgery on osseointegration of dental implants. Longer surgery time appeared to be related to higher failure of osseointegration (Wilcoxon p=0.03).
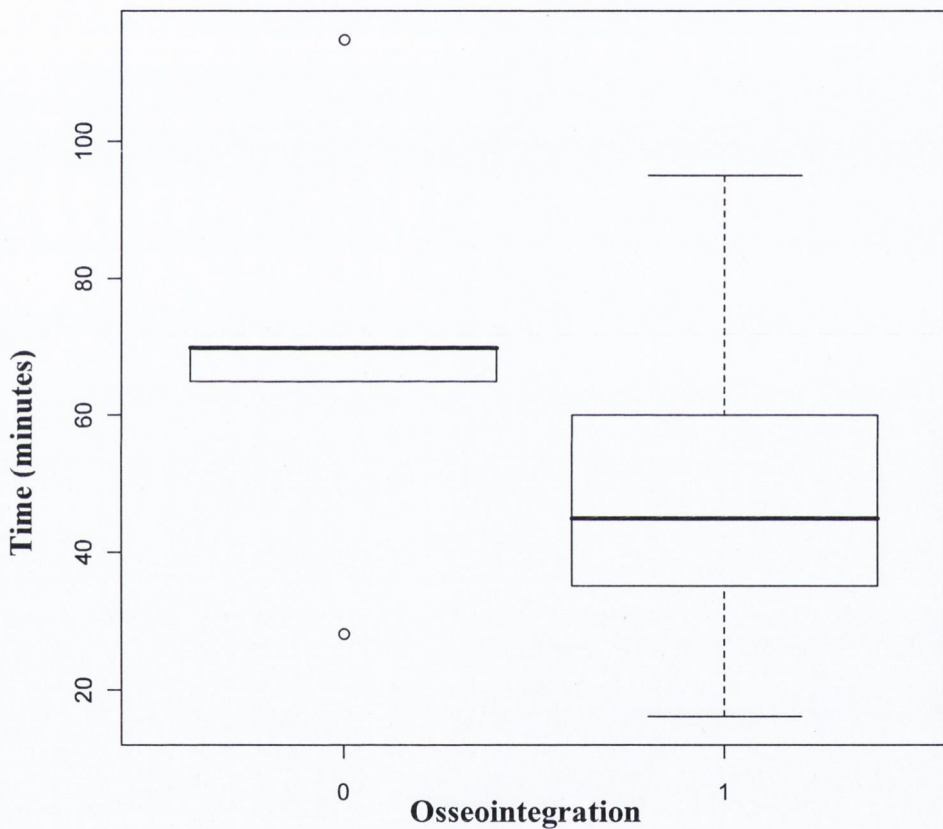
Fig. 4.44 **Box plot comparing the influence of the duration of surgery on osseointegration of the dental implants, Time in minutes on the y-axis, Osseointegration on the x-axis (1=osseointegration success; 0=osseointegration failed).**

4.15 Smoking on Osseointegration

Figure 4.45 demonstrates the influence of smoking staus on osseointegration of dental implants. No obvious difference was observed between the two groups.

	Osseointegration +ve	Ossoeintegration -ve
Non Smoker	38	4
Smoker	12	1

Table 4.12   Influence of smoking on osseointegration of implants
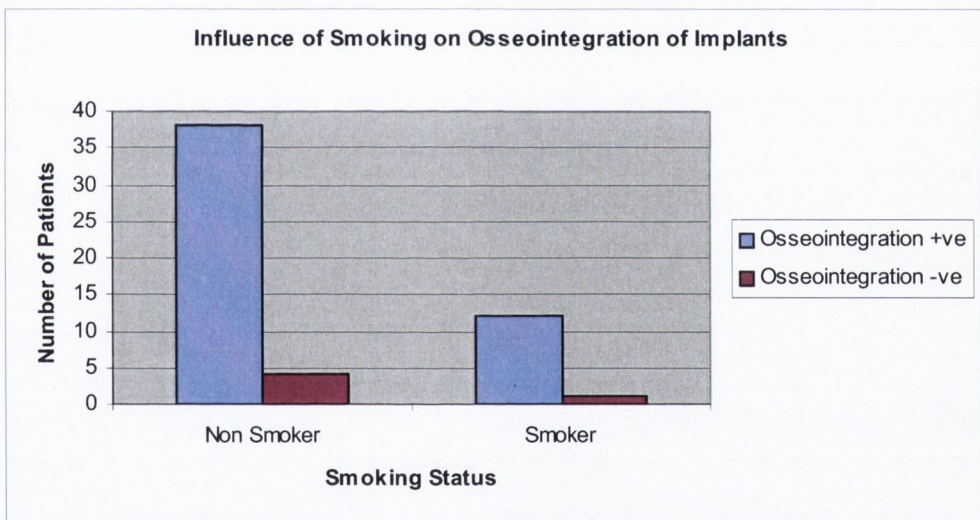
Fig. 4.45   Influence of smoking on osseointegration of implants

4.16 Influence of Site on Osseointegration of Dental Implants

Figure 4.46 demonstrates the influence of site of implantation on osseointegration of dental implants. No obvious difference was observed.

	Osseointegration +ve	Osseointegration -ve
Anterior Maxilla	24	2
Posterior Maxilla	13	0
Anterior Mandible	1	1
Posterior Mandible	12	2

Table 4.13   Influence of site on osseointegration of dental implants
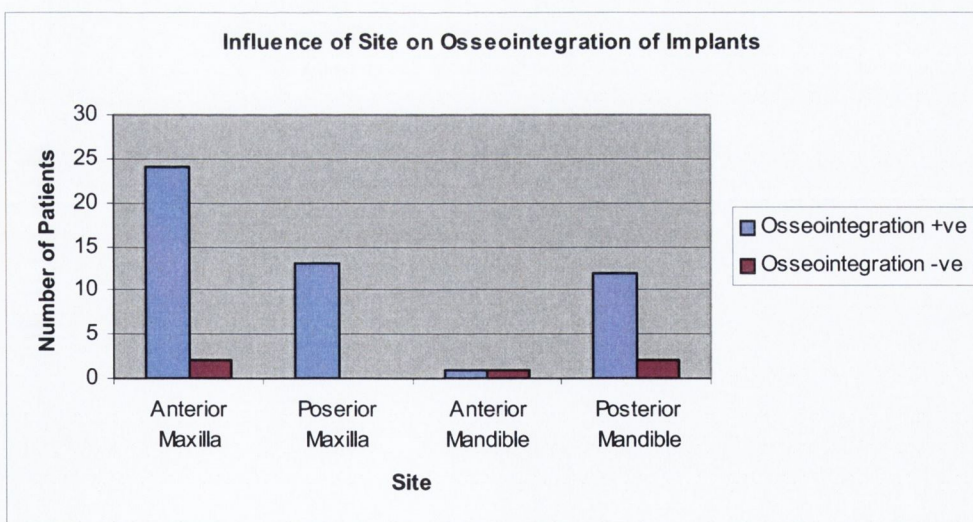
Fig. 4.46   Influence of site on osseointegration of implants.

4.17 Method on Osseointegration

Figure 4.47 demonstrates the influence of surgical method on osseointegration of dental implants. No obvious difference was observed between the three surgical methods.

	Osseointegration +ve	Osseointegration -ve
Two Stage	40	3
One Stage	3	1
Immediate	7	1

Table 4.14   Influence of method on osseointegration of implants
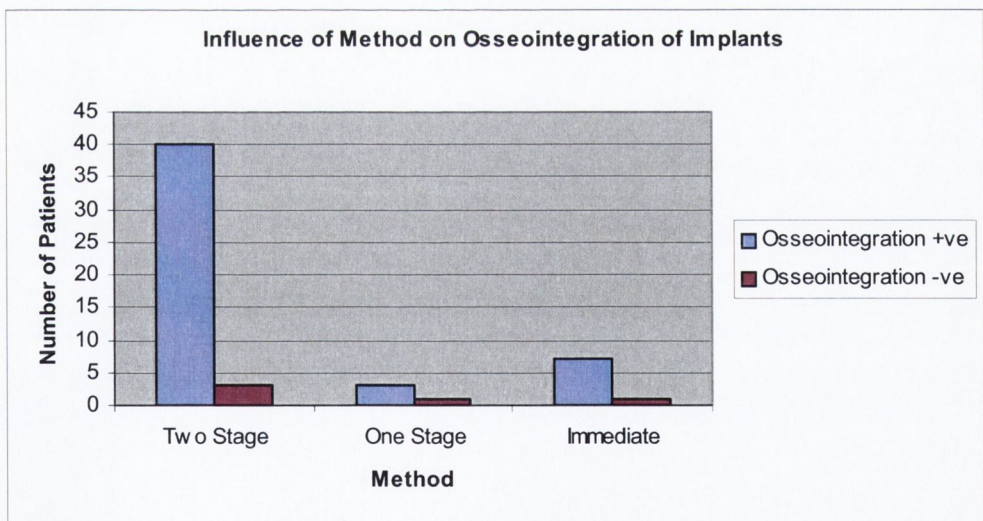
Fig. 4.47   Influence of method on osseointegration of implants.

4.18 Flap Advancement on Osseointegration

Figure 4.48 demonstrates the influence of flap advancment on osseointegration of dental implants. No statistically significant difference was observed between the two groups.

	Osseointegration +ve	Osseointegration -ve
No Flap Advancement	37	5
Flap Advancement	13	0

Table 4.15 **Influence of flap advancement on osseointegration of implants**
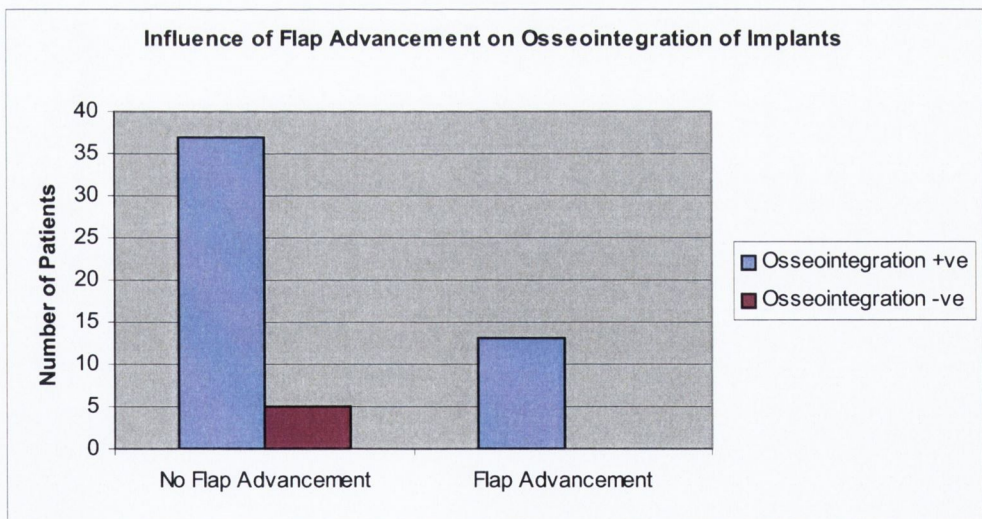
Fig. 4.48 **Influence of flap advancement on osseointegration of implants.**

4.19 Previous Bone Graft on Osseointegration

Figure 4.49 demonstrates the influence of previous alveolar bone graft on osseointegration of dental implants. No difference was observed between the two groups.

	Osseointegration +ve	Osseointegration -ve
No Bone Graft	39	5
Previous Bone Graft	11	0

Table 4.16   Influence of previous bone graft on osseointegration of implants
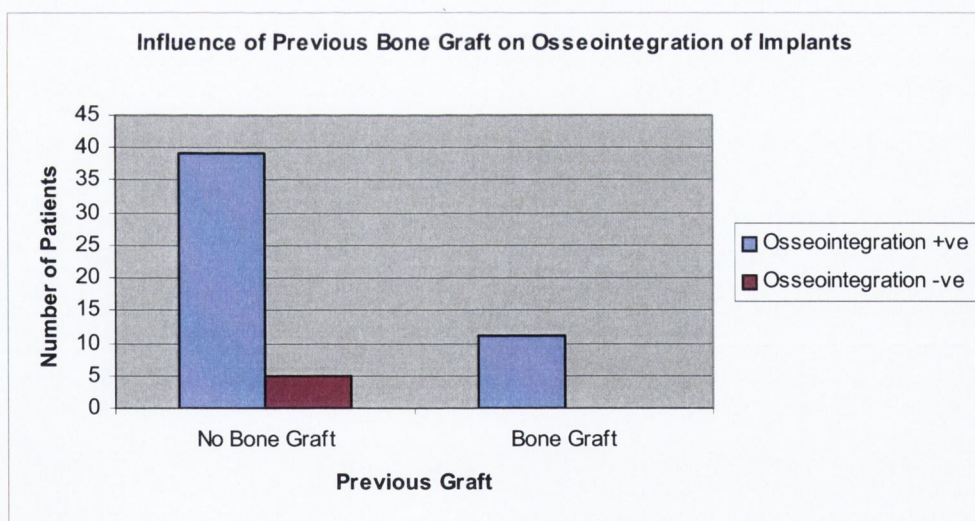
Fig. 4.49   Influence of previous bone graft on osseointegration of implants.

5. Discussion

The International Journal of Oral and Maxillofacial Implants, IJOMI, published a report in 2008 entitled "Guidelines for the Provision of Dental Implants" which cover the planning, surgical, restorative and maintenance phases of implant treatment. While it advises the use of proper aseptic surgical technique, nowhere does it mention the use of prophylactic antibiotics.

The use of prophylactic antibiotics in dental implant surgery remains controversial. This study was designed to evaluate the influence of prophylactic pre-operative antibiotics on osseointegration of dental implants, post-operative morbidity and post-operative pain and interference with daily activities. A prospective randomised controlled trial was conducted with patients either receiving 3 grams amoxicillin or a similar placebo drug pre-operatively. Patients were assessed 2 days and 7 days post-operatively for morbidity, pain and interference with daily activities. Osseointegration was assessed three to four months post-operatively or at second stage surgery.

The results of this study show that the use of prophylactic pre-operative antibiotics may result in higher survival of dental implants than when no antibiotics are used, 100% versus 82%. Five implant failures, 1 in each of 5 patients were reported in the placebo group, and none in the antibiotic group, p=0.05.

Previous studies have provided conflicting data with Dent et al. (1997) and Laskin et al. (2000) observing statistically significant improvements in implant survival when prophylactic pre-operative antibiotics were used. However it is unclear as to the randomisation procedure used in these trials. Other studies by

Gynther et al (1998), Esposito et al. (2008) and Abu-Ta'a et al. (2008), failed to show any statistically significant differences in implant survival when prophylactic pre-operative antibiotics were used. Two randomised controlled trials were conducted by Esposito et al. (2008) and Abu-Ta'a et al. (2008), and while they did not show statistically significant differences in implant survival, their results tended towards significantly higher implant survival in the antibiotic group. The Cochrane review on the use of prophylactic antibiotics and dental implant placement conducted meta-analyses of both trials and found a statistically significant difference in implant survival when prophylactic pre-operative antibiotics were used, with a risk ratio (RR) 0.22, 95% confidence interval (CI) 0.08 to 0.86. To illustrate the magnitude of the effect of implant failures, the number of patients needed to treat (NNT), i.e. given antibiotics to prevent one patient having an implant failure is 25 (95 % CI 13 to 100). This is based on a patient implant failure of 6% in patients not receiving antibiotics (Esposito et al. 2008). These results are in concord with those of the present study.

Duration of surgery was shown to be related to osseointegration of dental implants, with longer surgery times appearing to show a statistically significant higher rate of failures ($p=0.03$). This observation was not reported as having any difference in other studies.

Number of implants placed also appeared to significantly affect osseointegration of dental implants ($p=0.02$). Interestingly all patients that had failed implants had more than one implant placed simultaneously. Of the 5

failures, 4 patients had 2 implant placed and 1 patient had 3 implants placed. All other implants placed in these patients survived.

Operator experience may be a problem in the study with all operators in the study being periodontal postgraduate students and relatively inexperienced, albeit with the guidance of an experienced surgical supervisor. According to Laskin et al. (2000) who compared the survival of implants placed with and without prophylactic pre-operative antibiotics according to the surgeons' previous experience, those surgeons with greater than 50 implant placements prior to the study had a slightly higher implant survival rate (2.9%), when pre-operative antibiotics were used. This increase in survival rate was even more noticeable (7.3%), when less experienced surgeons, less than 50 previous implant placements used pre-operative antibiotics. This would suggest that as surgical skill increases with experience, there is less reliance on antibiotics for survival of implants. This should not be interpreted to infer however, that antibiotics will make up for poor surgical technique.

This study also used multiple implant systems, Osseotite® and OsseotiteNT®, Biomet3i, Florida, USA; Brånemark® TiUnite™ MKIII and MKIV, Nobel Biocare, Sweden; Ankylos®, Dentsply Friadent, Germany; Straumann® SLA, Straumann Implants, Switzerland. The majority of implants placed were Biomet 3i (65%). There were no statistically significant differences found for failure of osseointegration according to implant system. This is in agreement with the Cochrane review on different types of dental implants (Esposito et al. 2007).

Post-operative morbidity in this study defined as swelling, bruising, wound dehiscence, and suppuration, was assessed 2 and 7 days post-operatively. No statistically significant differences were found for any of the four outcome variables at either 2 or 7 days post-operatively except for bruising after 2 days, which appeared to be significantly higher in the placebo group (p=0.05). This same difference was not evident 7 days post-operatively (p=0.99). Wound dehiscence was rarely encountered, and almost equally in both groups. Suppuration was only seen in two patients, both of whom received a placebo pre-operatively, however this was not significant (p=0.49). More swelling was seen in the placebo group, again this did not show statistical significance after 2 days (p=0.65) and after 7 days (p=0.29).

While the above variables may be used to identify post-operative infection, in fact bruising and swelling are normal events in post-operative healing and should not be confused with infection. Wound dehiscence may be a sign of poor soft tissue handling during surgery, or indeed a reduced healing response from the patient as may be seen in smokers. Suppuration is a clear sign of infection and interestingly both patients who presented with post-operative suppuration, failed to achieve successful osseointegration of their implants and were from the placebo group.

Infection is defined as "invasion of the body tissues by pathogenic organisms" (American Academy of Periodontologoy. *Glossary of Periodontal Terms*, 2001). Applying this definition clinically has led various investigators to differ in their criteria to describe the presence of an infection. In surgical wounds, a comprehensive definition of what constitutes a clinical infection may be one

that is characterized by delayed onset, suppuration or presence of a fistula, possible pain, swelling, redness and heat or fever greater than 38°C (Sawyer & Pruett 1994).

Paracetamol was chosen as the sole analgesic to be used by the patients in an attempt to standardise the post-operative pain medication used so as to improve reliability of the results. It has been shown to be effective in relieving pain with a low incidence of adverse effects (Moore et al. 1998). It has also been shown to be an effective analgesic in the control of post-operative dental pain in a number of clinical trials (Bentley & Head 1987; Mehlisch 1990; Kiersch et al. 1994).

Post-operative pain was subjectively measured by the patients using visual analogue scale questionnaires for one week, and also by keeping a record of the number of paracetamol 500mg analgesic tablets taken. While higher pain scores were recorded by the placebo group the difference seen after 2 days post-operatively was not significant (p=0.10). However the difference appeared to reach statistical significance after 7 days (p=0.01). A higher number of analgesics were also taken by the placebo group after 7 days and again this appeared to be statistically significant (p=0.008). This difference could be due to an improved healing response with the use of antibiotics, which impacted favourably on the pain experience by the patient.

Previous studies comparing the effect of antibiotics on post-operative pain with dental implant surgery are scarce. In agreement with the present study, Abu-Ta'a et al. (2008) in a prospective randomised placebo-controlled trial,

observed that the use of prophylactic antibiotics resulted in statistically significant lower patient subjective assessment of post-operative pain using visual analogue scale questionnaires.

A similar outcome was seen when looking at the influence of prophylactic pre-operative antibiotics on the patients' subjective experience of the interference with daily activities. Again higher scores were recorded by the placebo group, and while the difference was not significant after 2 days (p=0.15), this difference seemed to show statistical significance after 7 days (p=0.01). Again this difference could be due to an improved healing response with the use of antibiotics, which impacted favourably on the interference with daily activities experienced by the patient.

Those patients with implant failure reported higher pain (VAS scores) after 2 days (p=0.003), and after 7 days (p=0.0005). Those patients with implant failure also reported higher pain (number of analgesics used) after 7 days (p=0.001). Those patients with implant failure also reported higher interference with daily activities (VAS scores) after 2 days (p=0.005). This in itself is an interesting and unique finding, perhaps suggesting a role for post-operative infection in these patients who were not given prophylactic antibiotics. Thus high levels of pain and interference with daily activities shortly after surgery may be an important indicator of implant failure.

Longer duration of surgery showed a significant but modest correlation with post-operative pain (VAS scores) after 2 days (r=0.3). Longer duration of surgery also showed a significant but modest correlation with post-operative

pain (number of analgesics used) after 7 days (r=0.4). Longer duration of surgery also showed significant but modest correlations with interference with daily activities after 2 days (r=0.3) and after 7 days (r=0.4).

Longer incision length showed significant but modest correlations with interference with pain (VAS scores) after 2 days (r=03) and after 7 days (r=0.3). Longer incision length also showed a significant but modest correlation with interference with pain (number of analgesics used) after 7 days (r=0.4). Longer incision length also showed significant but modest correlations with interference with daily activities (VAS scores) after 2 days (r=03) and after 7 days (r=0.3).

Hashem et al. (2006) conducted a prospective study to assess pain and anxiety following dental implant placement. The authors concluded that implant placement is a mild to moderately painful and anxiety producing procedure, and that some limitation of daily activities and post-operative symptoms are expected to occur, especially during the first 3 post-operative days.

There are still no clear guidelines on the correct choice of antibiotic drug, the correct dose, and the correct duration. While most studies have focused on whether the antibiotic is required or not, Lindeboom et al. (2006) compared 2g of penicillin versus 600mg clindamycin as a single pre-operative dose in patients treated with block grafts harvested form the ramus of the mandible and covered with resorbable membranes. No implants were placed in the study and patients were followed up for eight weeks. No statistically significant differences were observed for post-operative infections. It is not clear whether

an antibiotic that binds to bone such as tetracycline, would provide better results, albeit that tetracycline is bacteriostatic agent. Most antibiotic prophylaxis regimens are based on the American Heart Association guidelines for prevention of bacterial endocardits, either the 1990 guidelines recommending the use of 3g amoxicillin, or the 1997 guidelines recommending the use of 2g amoxicillin as a single pre-operative dose (Dajani et al. 1990; Wilson et al. 2007).

Studies in the literature report that the use of prophylactic post-operative antibiotics are not warranted (Burke 1961; Stone et al. 1979; Binahmed et al. 2005; Lindeboom et al. 2005). There are public health concerns regarding prolonged antibiotic usage. Whereas there is little chance of inducing resistant microbial strains with only a pre-operative protocol of a large dose of antibiotic, this risk is higher for more long-term use (Laskin et al. 2000; Esposito et al. 2008).

Antibiotic prescribing practices in both hospital and private practice settings need to be addressed, not only for dental implant procedures, but also for the full spectrum of periodontal and dentoalveolar surgical procedures. While infection rates remain low even without the use of antibiotics, the routine prescription of antibiotics remains high (Powell et al. 2005).

The community remains convinced of the power of antibiotics. Patients may often demand antibiotics and even feel inappropriately treated if these are not prescribed. It can become problematic when these patients are supported by their general medical practitioners and general dental practitioners who have

not kept up to date with the latest evidence (Lawlor et al. 2005). This can in turn make the surgeon look incompetent to the patient and so to avoid this confusion prescribing the antibiotic is often simpler. However, prescription of antibiotics without medical indication is not justifiable.

The design of this study had strict admission criteria so that only medically fit and well individuals could be included. This was based on the assumption that their host defences were strong enough to prevent any post-operative infection. In patients with a significant reduction in host defences the risk of infection increases. For patients with HIV/AIDS undergoing dentoalveolar surgery, this has been quantified as a ten-fold increase in infection rate (Dodson et al. 1994). Also, patients taking immunosuppressants for organ transplants or malignancy will have an increased risk of infection. Patients suffering from poorly controlled diabetes mellitus may also have an increased risk of developing post-operative infections due to their impaired immune response. Patients that have undergone therapeutic irradiation are at risk of developing osteoradionecrosis following any type of dentoalveolar surgery. Patients who are taking bisphosphonate medication, especially intravenous bisphosphonates are at risk of developing osteochemonecrosis spontaneously, but usually following dentoalveolar surgery. All these patients require antibiotic prophylaxis both pre- and post-operatively, and so the results of this study do not change the protocols currently being followed for their treatment.

Within the limitations of this study the following can be concluded:

- Pre-operative antibiotic prophylaxis may improve the survival rate of osseointegration of dental implants.

- Pre-operative prophylactic antibiotics may reduce pain and interference with daily activities post-operatively as reported subjectively by the patient.

- Pre-operative prophylactic antibiotics may reduce post-operative pain as measured by the number of painkillers taken.

- High levels of post-operative pain and interference with daily activities following implant surgery may be an indication of failing osseointegration.

- Pre-operative antibiotic prophylaxis does not seem to significantly reduce the incidence of post-operative swelling, bruising, wound dehiscence, and suppuration, apart from a beneficial effect on bruising after 2 days.

Overall from the evidence presented in this study, it would seem that the use of pre-operative prophylactic antibiotics may be beneficial both in terms of implant survival and patient comfort.

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7. Appendix

7.1   Statement on nature of the study for patients.

Date

Dear Patient,

We would like to inform you of a study in which we would like you to participate in. It is thought that antibiotics given prior to implant surgery reduce the number and severity of complications such as swelling, pain, infection and implant integration failure. However, the evidence to support this is somewhat incomplete. Some similar studies have shown no marked advantage of taking antibiotics, one conducted with implants the other analysing complications occurring after wisdom tooth removal. Considering that prescription of antibiotic may lead to the development of bacteria that may not be affected by this antibiotic, overuse of antibiotics is undesirable.

If you decide to participate you will be randomly assigned to one of two groups:

1. Patients receiving 3 gr of Amoxil prior to your implant surgery.

2. Patients receiving the same amount of a placebo prior to your implant surgery.

The group you will be assigned to will not be known by you or the investigator until completion of the study.

Two independent dentists will examine you twice in the first week after your surgery to assess any complications. This data are then analysed. You will be

asked to keep a diary of the number of painkillers (Paracetamol 500mg) used for the following week. You will also be asked to keep a diary of the pain experience, and the interference with daily activities for the following week. . These data are then analysed. The vast majority of complications, which may be experienced, are not severe and transient in nature. Personal details at no stage will be published or reviewed by persons outside of this clinical trial or competent board over viewing the conduct of the research.

At this stage I may kindly ask you to reflect on this information and encourage you to ask any question you feel to be important.

Thank you for your kind assistance.

Yours sincerely,

DR. Rory Nolan

Postgraduate Student

PROFESSOR NOEL CLAFFEY

Dean of the Dublin Dental School & Hospital

Department of Restorative Dentistry & Periodontology

7.2   Consent Form

Title of Study: The influence of prophylactic antibiotic administration on post-operative morbidity and osseointegration in dental implant surgery.

Name of Institution: Dublin Dental School & Hospital

Research Director: Professor Noel Claffey

Research Conductor: Dr Rory Nolan

Phone Number and Contact Details: 087 7438156 rory.nolan@dental.tcd.ie

Participant

I have read the attached information sheet on the above project dated and have been given a copy to keep. The information has been fully explained to me and I have had an opportunity to ask questions about the project and understand why the research is being done and any foreseeable risks or consequences involved. I also understand that no guarantees can be given about possible results.

I give permission for my medical records to be looked at and information taken from them to be analyzed in the strictest confidence by the relevant and responsible people (Study Team) or from organizations supervising the research. I have been told that all medical information /data pertaining to me will be protected by the principles of confidentiality and both national and EU data legislation.

Date (Patient):   Date (Dentist):

Name (Patient):   Name (Dentist):

7.3   Randomisation

Envelope Number   **Contents**

7.4   Data Collection Sheet – Dentist 1

Patient Name: **Date:**

Date of Birth: **Surgeon Name:**

Chart Number: **Implant System:**

Age:

Gender:

Smoker: Yes   No   Cigarettes per day:

Site of Implant: Ant. maxilla   Post. maxilla

                         Ant. mandible   Post. mandible

Method: Immediate implant

                 1 Stage

                 2 Stage

Length and diameter of implants:

Previous bone graft: Yes   No

Flap advanced: Yes   No

Partial Denture: Yes   No

Number of implants: 1   2   3   4

Amount of LA: 2ml   4ml   6ml   8ml   10ml

Length of incision (cm):   <1   <2   <3   <4   >4

Duration of surgery (mins):

7.5　Data Collection Sheet – Dentist 2

Patient Name:　　　　　　　　Date:

Date of Birth:　　　　　　　　Surgeon Name:

Chart Number:　　　　　　　　Implant System:

Examination Timepoint	2 days post-op	7days post-op
Swelling		
• None		
• Mild		
• Moderate		
• Severe		
Suppuration		
• Absent		
• Present		
Bruising		
• Absent		
• Present		
Wound Dehiscence		
• Absent		
• Present		

7.6 Data Collection Sheet – Patient 1

Patient Name: **Date:**

Date of Birth:

Chart Number:

Please mark the line at a position between the two extremes to represent the level of pain that you experienced **during implant surgery:**

No Pain _____Intolerable Pain

Please mark the line at a position between the two extremes to represent the level of pain that you experienced for:

a) Local anaesthetic

No Pain _____Intolerable Pain

b) Incision

No Pain _____Intolerable Pain

c) Drilling

No Pain _____Intolerable Pain

d) Implant Placement

No Pain _____Intolerable Pain

e) Suturing

No Pain _____Intolerable Pain

Patient Signature:

7.7   Data Collection Sheet – Patient 2

Patient Name: **Date:**

Date of Birth:

Chart Number:

1.   Pain.

Please mark the line at a position between the two extremes to represent the level of pain that you experienced after implant surgery on day:

Day   1   2   3   4   5   6   7   8

No Pain _____Intolerable Pain

2.   Interference with daily activities.

Please mark the line at a position between the two extremes to represent how the pain that you experienced after implant surgery interfered with your daily activities on day:

Day   1   2   3   4   5   6   7   8

No Pain _____Intolerable Pain

Patient Signature:

7.8 Data Collection Sheet – Patient 3

Patient Name: **Date:**

Date of Birth:

Chart Number:

Please indicate the number of 500mg Paracetamol tablets taken during:

Surgery – Day 2

Day 3 – Day 7

Patient Signature: