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WJO covers topics concerning arthroscopy, evidence-based medicine, epidemiology, nursing, sports medicine, therapy of bone and spinal diseases, bone trauma, osteoarthropathy, bone tumors and osteoporosis, minimally invasive therapy, diagnostic imaging. Priority publication will be given to articles concerning diagnosis and treatment of orthopedic diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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EDITORIAL

Economic factors in the future delivery of spinal healthcare

Vincent J Rossi, Junyoung Ahn, Daniel D Bohl, Ehsan Tabaraee, Kern Singh

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Abstract

The current trajectory of healthcare-related spending in the United States is unsustainable. Currently, the predominant form of reimbursement is the form of a fee-for-service system in which surgeons are reimbursed for each discrete unit of care provided. This system does factor the cost, quality, or outcomes of service provided. For the purposes of cost containment, the bundled episode reimbursement has gained popularity as a potential alternative to the current fee-for-service system. In the newer model, the spinal surgeon will become increasingly responsible for controlling costs. The bundled payment system will initially offer financial incentives to initiate a meaningful national transition from the fee-for-service model. The difficulty will be ensuring that the services of surgeons continue to be valued past this initiation period. However, greater financial responsibilities will be placed upon the individual surgeon in this new system. Over time, the evolving interests of hospital systems could result in the devaluation of the surgeons' services. Significant cooperation on behalf of all involved healthcare providers will be necessary to ensure that quality of care does not suffer while efforts for cost containment continue.

Key words: Affordable care act; Spine surgery; Economics; Future; Access; Payments; Reimbursement

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Core tip: Following the enactment and implementation of the patient protection and affordable care act, healthcare providers will witness significant changes in how payments are made for their services. In this editorial, the authors describe the potential benefits and the risks associated with a transition toward the bundled reimbursement system for patients and spine surgeons alike.

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EDITORIAL

During 2013, healthcare-related spending in the

United States grew by 3.6% accounting for $2.7 trillion dollars and 17.3% of the gross domestic product (GDP)[1]. It is widely accepted that the current trajectory of healthcare-related spending in the United States is unsustainable. However, less agreement exists regarding the optimal approach to improve its sustainability. The current fee-for-service payment system is cited as a potential source of escalating healthcare costs and wasteful spending[2,3]. The Patient Protection and Affordable Care Act (2010) attempts to address this issue while improving the quality and access[4]. Through provisions outlined in the law, direct endorsement by the president[5], and several demonstration projects[6,7], the bundled episode payment system has gained popularity as a means to contain healthcare-related costs.

There is a spectrum of potential financial models for health care reimbursement. At one extreme is the fee-for-service model, which is currently the predominant model in the United States. This model limits the financial risk for providers. Healthcare providers are reimbursed for each discrete component of care that they provide, regardless of cost, quality, or outcome. On the opposite end of the spectrum is the concept of global payments. This is a capitation model in which a single amount is allocated for each episode of care independent of the extent of health-related needs. This model exposes providers to a substantial amount of financial risk in which the spine surgeon could be paid incrementally less depending on the utilization of resources.

The concept of bundled episode payments exists on a financial spectrum between the fee-for-service and global payment systems. In the bundled episode payment model, reimbursements occur for an entire episode of care. This model is most applicable to procedures in which a predetermined reimbursement could potentially be disbursed for the care episode and for any ancillary services provided over a predetermined time period. In this model, a single payment is given to providers to divide among services and materials. This single payment is intended to cover physician fees, operating costs, the inpatient stay, physical therapy following discharge, and any costs associated with complications or readmissions to the hospital.

Reimbursement per care episode has been an entity in the healthcare system since the implementation of Medicare's diagnosis related groups (DRGs)[8]. In this system, reimbursements are based upon admissions for specific diagnoses, such as congestive heart failure or diabetes. In addition, the model of a lump sum bundled payment for care has been present in Health Maintenance Organizations (HMO) for decades. However, "bundling" payments for a given procedure and all care received within a specific time period is a relatively new model that has gained significant traction in recent healthcare reform discussions.

The strongest theoretical advantage of the bundled payments is cost containment. The incentives of all providers are aligned to reduce costs in order to share in the potential savings. This reduces the incentive for wasteful use of medical resources, especially those that may not significantly improve patient care. Bundled payments place greater incentive for providers to control avoidable and costly complications during the postoperative period.

Critics would point out that a disadvantage of the bundled payment system is that hospitals and providers will unfairly select healthier patients or adjust indications of procedures in order to maximize profit. In addition, there are concerns that in an attempt to reduce costs, surgeons may favor cheaper, less technically complex procedures in replacement of more costly procedures that have demonstrated superior outcomes[9].

At this time, there is significant momentum to establish bundled payments as the primary means of reimbursement, particularly for elective procedures with well-defined outcomes and consistent involvement of particular ancillary services. This is especially attractive for common, elective orthopedic and spine procedures. Many institutions anticipate moving to this reimbursement method. As such, much effort is being placed on research regarding the cost and financial variability that occurs within them[10].

The financial implications of bundled payments for surgeons are significant. For example, surgeons would clearly take on greater financial risk. Such risk has two components. The first is probability risk, which refers to random events that occur as a result of uncontrollable external and genetic factors related to the patient[10]. The second is technical risk, which refers to risk that is a direct consequence of the intervention and care during the episode[10]. These risks include postoperative complications, urinary tract infections, and readmissions. In an ideal system, any penalties to providers should relate to technical risk; however, the distinction between technical risk and probability risk is not always defined. For instance, the impact of factors such as patient non-adherence to medical and therapeutic regimens, preoperative illness severity, and poor patient lifestyle choices is hard to dichotomize clearly into either of the two classifications. The providers will inevitably take on at least a proportion of this risk as it is not only difficult to clearly define them, but would be administratively unfeasible to do so.

The increased financial risk undertaken by surgeons will need to be offset with the potential for larger financial gains. In order to protect providers, a proper risk corridor must be established. A risk corridor limits the profits and losses above or below a given percentage from the net neutral position[11]. By defining the range of profits and losses, surgeons are protected from catastrophic financial losses while any

exuberant gains are limited.

In the context of the increasing demand for cost control in spine surgery, recent trends have emerged. One such trend is the movement towards performing surgery in ambulatory surgery centers (ASC). ASCs aim to avoid the expensive costs of hospitalization, which have historically been one of the largest contributors to the total cost of a care episode[12]. The shift towards ASCs increases the predictability of the related costs while reducing the potential of developing costly complications during a hospital admission. With recent advances in outpatient anesthesia and pain management protocols, avoiding hospitalization following spine surgery is becoming increasingly feasible for selected procedures. However, potential complications of spine surgery will require this paradigm shift to proceed cautiously as to not compromise patient care solely based upon the idea of cost containment.

In addition, criticism regarding the use of implants and biologics may increase as their utilization have been the source of increasing costs[7]. There will be more discretion regarding the use of newer, more costly designs that may only benefit marginally over traditional options. Procedures such as a simple decompression for stable degenerative conditions may also gain popularity in place of a more costly fusion procedure if the reimbursements within the bundled payment for both types of procedures are comparable.

The specifics of when the changes to the healthcare system will occur and how they will impact surgeons' practices remain unclear. However, the fact that the healthcare system is changing has never been more certain. All surgeons should anticipate these changes and be active participants in the discussion in order to properly advocate what is best for their patients and their respective specialties. The shift in payment systems should be a beckoning call for surgeons to unite their interests in order to clearly establish the value of their services to the hospital and the society at-large.

The bundled payments system could shift the physician fees and salaries onto the institution. In an effort to better predict costs, hospitals will come under pressure to hire salaried surgeons. In such a system, hospital administrators will determine the salary of the surgeon. This may ultimately appraise the value of the surgeons' services within the episode of care. As such, reimbursement to physicians will be strongly correlated with the price at which the hospital is reimbursed for the bundled care episode. As the financial uncertainty of the national health care system continues, decreasing bundle prices will be an appealing way to cut costs on national health spending. This cost cutting measure may prompt administrators to react by reducing payments to surgeons, especially once costs related to postoperative care have reached economies of scale in which additional incremental savings may no longer be attainable.

In conclusion, surgeons have the potential to gain financially in the short-term by participating in the bundled payment system. This system will initially require tempting financial incentives in order for the country to initiate a meaningful national transition from fee-for-service. The difficulty will be insuring that the services of surgeons continue to be valued past this undetermined period. It appears possible that greater financial risk burden will be placed upon the individual surgeon in this new system. Over time, physicians may be placed in increasingly vulnerable positions in which the desires of the hospital systems result in devaluing of the services provided by the surgeon. Significant cooperation on behalf of all involved healthcare providers will be necessary to ensure that quality of care does not suffer while efforts for cost containment continue.

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EDITORIAL

Importance of balance and profile in adult spinal reconstruction

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Abstract

Long before its current understanding, the concept of balance was common among spine surgeons dealing with deformities, but it was a hard one to transfer to clinical practice. Thanks to the pioneering work of Duval-Beaupere and followers, the idea of balancing the sagittal contour of the spine has gained scientific status and is now in the armamentarium of the skilled surgeon as the single most important tool to achieve superior clinical results in adult spinal deformity surgery.

Key words: Sagittal balance; Sagittal profile; Adult spinal deformity; Anterior fusion; Posterior fusion

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Core tip: Adult spinal reconstruction is set to become the emerging trend in the next years in spinal surgery. Failure of restoration of adequate spinal balance and profile in the sagittal plane is now recognised as the single most important factor determining inadequate improvement in quality of life in adult patients undergoing reconstructive surgery for spinal deformity.

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INTRODUCTION

Twenty years ago the concepts of pelvic tilt and incidence were scholar work for researchers who did not seem to have a solid grip on clinical matters[1]. Time, though, brings clarity to scientific matters. It became progressively apparent and accepted that patients undergoing fusion for degenerative deformities did not do well when their sagittal rather than coronal balance was less than restored[2]. Alleged reasons for these failures included natural history[3], junctional degeneration[4] and bone-implant interface failure[5] to name a few. It was only when surgeons started to learn the rules of spino-pelvic parameters and to apply them to patients that reports on adult spinal deformity surgery changed their grim faces into a more optimistic appearance[6].

The spinal community is set to be invaded by

ageing patients who demand increasing performances as their life expectancy and, sadly, the prevalence of their acquired deformities both increase. While the current scenario is dominated by the obsessive research of balance through the use of spinal osteotomies[7], the next will see the research of lesser invasive methods of anterior and posterior reconstruction that would not be at the expense of obtaining a solid and lasting fusion[8]. Open questions are issues about costs and complications of this most complex aspect of clinical medicine[9-11]. Aim of this paper is to set the scene of current and future trends in adult spinal deformity (ASD) surgery by analysing the potentially most important recently published papers on the subject.

We analysed English edited papers on ASD surgery through PubMed in the years 2000-2014 with attention to parameters that closely related to surgical outcomes[2-9]. Eleven papers were included in the analysis because of their clinical relevance to the subject[2-12]. All of them are retrospective case series or reviews limiting the value of their evidence to lower levels. Nevertheless, they represent the current golden standard of practice and the basis for future trends.

Criteria to include these papers in the analysis included: (1) Minimum follow-up of one year; (2) Objective quality of life measurements performed preoperatively and at follow-up; (3) Description and rating of complications into major and minor ones; (4) Description of type and site of osteotomies; and (5) Description of preoperative and follow-up sagittal spino-pelvic measurements.

Despite the variability of inclusion criteria on age, comorbities, severity of deformities and surgical techniques, the one issue that becomes apparent from the analysis of this literature is the obsessive description of spino-pelvic parameters as the most important feature correlating with clinical results.

The methods to achieve postoperative balance which are described in the papers include posterior wedge (chevron like or Ponte or Smith Petersen) osteotomies in case of non-rigid deformities with mobile discs; pedicle subtraction osteotomies and/or vertebral column resections in case of severe and rigid deformities and anterior or lateral interbody fusion techniques to improve the chance of a lasting correction of the deformity.

DISCUSSION

The group of Duval-Beaupere were the first to conceive the importance of pelvic parameters in the sagittal profile of the spine[1]. Before this paper gained widespread acceptance, most surgeons dealing with adults as well as paediatric deformities only concentrated on the coronal profile of the spine as a marker of their efforts. This is just one of the many possible examples of how tradition and lack of evidence may impair the practice of medicine. Fortunately, the translation of this pioneering work into practical guidelines led to increasingly common reports on how the sagittal profile impacts on daily living of affected patients, and this trend does not seem to stop on either sides of the Atlantic Ocean[2,3,9].

Many are the parameters of spinal balance described so forth[4], but three deserve particular attention, *i.e.,* Pelvic Incidence (PI), Pelvic Tilt (PT) and Sacral Slope (SS).

PI represents the width of the pelvis as seen on a lateral radiological view. PI is a fixed parameter for every person at the end of skeletal growth and determines the possibility of the spine to accomodate for degenerative changes that occur with ageing. PT represents the possibility of the pelvis to rotate on the femoral heads to accomodate for these changes. During backwards rotation, the PT increases and this movement is known as pelvic retroversion, while the opposite rotation is known as anteversion. Both retro and anteversion influence the SS, *i.e.,* the inclination of the sacrum in relation with the ground. PI, PT and SS are in mutual relationship according to the following equation: PI = SS + PT.

For instance, a PI higher than the average 52° predisposes to degenerative spondylolisthesis while a lower PI may lead to early degenerative disc disease and disc herniation (for full explanation of these features please refer to the paper by Rossouly and Nnadi[4]). On a practical ground, one of the lessons to be learned is that fusion of the lumbar spine should aim at a value of Lumbar Lordosis (LL) at least equivalent to that of PI or within 9 degrees of it[2,4]. Another important concept is that balance and profile should never be confused. A balanced spine is one that keeps its equilibrium without undue muscular efforts, pain or deformity, irrespective of its profile.

In fact, the sagittal profile of healthy adult volunteers has been studied and sub-classified into four types according to the level of the inflection point between the thoracic and the lumbar tracts of the spine[4]. These four types are rather simple keep in mind and should be used as a reference template in planning osteotomies and correction of ASD, in order to respect the original shape, *i.e.,* profile, of the individual spine[3,4]. In a simplistic way, the last important concept is that 70% of all lumbar lordosis, irrespective of the spinal profile, is concentrated between L4 and S1. As these levels are the ones that are most commonly addressed by surgical reconstruction, failure to recognise and restore any loss of lordosis would inevitably lead to spinal imbalance and trigger decompensation with aging[3].

Means to achieve the above goals are without any doubt advanced imaging techniques like EOS, a revolutionary tool using slot scanning low emission X ray bidimensional representations of the deformed spine and of the relative spinopelvic parameters[10]. EOS is able to record simultaneously postero-anterior and lateral X ray images allowing for tridimensional

reconstruction if desired. Another important feature is the ability if EOS to acquire full lenght bodily images, avoiding the need to stitch multiple images as needed in traditional X ray pictures. The quality of EOS pictures is similar to digital radiography and in tridimensional reconstructions it allows multiplanar views of the deformed spine (as well as of the appendicular skeleton if needed). EOS will become more widely available in time but is nowadays an expensive tool that many centers cannot afford. Nevertheless, even in the absence of EOS surgeons should make every effort to obtain high quality full spine standing AP and lateral X-rays including the hips and 10 cm of the femurs along with flexed elbows in order to study the proximal thoracic tract. Once adequate imaging is obtained, the planning of corrective osteotomies can take place. Accepted techniques are wedge, pedicular and vertebral column resection osteotomies. These are all performed by a posterior approach and rely on solid pedicle instrumentation - two to three levels above and below - to obtain immediate corrective power, unfortunately at the expense of significant morbidity[5,11]. Major complications including death, permanent paralysis, pseudoarthrosis, proximal junctional failure and infection may affect up to 60% of treated patients and are largely dependent on age, degree of sagittal imbalance and medical comorbidities at the current state of knowledge[3-6,11]. In addition, there seems to be wide variability in revision rates among centers treating different volumes of patients[12]. Hence, the role of minimally invasive anterior (and posterior) support in ASD surgery is increasingly reported[7,8] and its efficacy awaits the test of time.

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EDITORIAL

Placebo effect in osteoarthritis: Why not use it to our advantage?

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Abstract

Osteoarthritis is a major cause of pain and reduced quality of life in the elderly, as well as a major economic burden. Unfortunately, there is no currently effective therapeutic strategy to prevent the progression of Osteoarthritis, and its treatment poses a great challenge to the medical community. Most of the treatment modalities currently available for osteoarthritis have small to moderate effect sizes, according to main meta-analyses and treatment guidelines. On the other hand, literature has demonstrated that placebo is considerably effective. The present article discusses the history of placebo effect and its scientific evidence, comments on ethical issues and provides insights about how it may be used to our advantage when treating osteoarthritic patients.

Key words: Osteoarthritis; Placebo; Treatment

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Core tip: Osteoarthritis is a major cause of pain and reduced quality of life in the elderly population, as well as an economic burden. Unfortunately, there is no currently effective treatment, and most of them show small to moderate effect sizes, according to main meta-analyses. On the other hand, literature has demonstrated that placebo has a considerable effect size in osteoarthritis clinical trials. So why not use it to our advantage?

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INTRODUCTION

Osteoarthritis (OA) is a major cause of pain and reduced quality of life in the elderly[1]. It is also an economic burden, associated with high direct and indirect health-related costs, as well loss of adjusted life years[2]. Unfortunately, there is no currently effective therapeutic strategy to prevent the progression of the disorder, and its treatment poses a great challenge to the medical community[3].

Most of the treatment modalities currently available for OA have small to moderate effect sizes (ESs),

according to main meta-analyses and treatment guidelines[4-8]. An ES of 1 indicates that the mean at endpoint is 1 standard deviation below the mean at baseline[9]. In terms of symptomatic improvement, an ES around 0.2 implies a minor benefit, 0.5 indicates mild effect and 0.8 and higher indicates a major effect[9].

A 2011 meta-analysis found only moderate benefits of self-management programs on measures of arthritis-related pain and disability[4], with estimated ES for pain relief of 0.06 (0.02-0.10)[4]. Acupuncture (ES = 0.28)[5], exercise (ES = 0.34)[6], weight management (ES = 0.20)[10], paracetamol (ES = 0.13)[11], NSAIDs (ES = 0.37)[12] and viscosupplementation (ES = 0.37)[13] are another examples of recommended non-surgical treatments for OA, with small to moderate ESs. In light of the current complete lack of structure modifying treatments, there is a need to reassess the current paradigm.

In 2008, a systematic review to examine the placebo effect and its potential determinants in the treatment of OA has demonstrated that placebo is effective with considerable ES[14]. For pain relief the overall ES was 0.51 [95% confidence interval (CI): 0.46 to 0.55] for placebo, but nearly zero for patients who were in "no treatment" groups. Such large effect is certainly a surprising and impressive finding. So why not use it to our advantage?

HISTORY OF PLACEBO

Placebo is the Latin word of "I will please". In the thirteenth century, hired mourners often repetitively chanted the 116 psalm "I will please the Lord". The term "placebos" became popular and referred to their fake behavior[15]. Until 1945, placebos were used by physicians as a "morally" useful but innocuous tool without ethical issues[16]. When paternalistic ethics prevailed, placebo was considered "The Humble Humbug", a means of reinforcing a patient's confidence in his recovery, to comfort patients with terminal conditions, "especially those low in intellect"[17,18].

After World War Ⅱ, the use of the double-blind randomized controlled trial (RCT) began to establish itself as the standard method for "rational therapeutics", and the placebo went through a dramatic transformation, imbued with powerful therapeutic effects that could mimic potent drugs[16]. This, along with effective drug discovery, brought concern about the ethics of its use. The modern concept of placebo was consolidated a few years later with Beecher's paper entitled "The Powerful Placebo"[19]. In this analysis, the author found evidence that placebos have an average high therapeutic effectiveness of 35%[19]. He also stated that "the total drug effect is equal to its active effect plus its placebo effect"[19]. From this moment, anything aside the predictable cause and effect outcome was considered "placebo effect", or "placebo response", a new and much larger concept of placebo.

PLACEBO RESPONSE

The placebo response can be defined as the symptomatic improvement provenient from a treatment or intervention that does not result from the substance or intervention itself, but is due to the therapeutic ritual, context, expectations or any other patient, caregiver or environmental factor involved in the treatment. It's a very complex and omnibus concept, previously defined by other authors as "symptomatic improvement on receiving any inert/non-therapeutic (placebo) intervention(s) compared to those who do not receive it"[20] or "a change in a patient's illness attributable to the symbolic import of a treatment rather than a specific pharmacologic or physiologic property"[21]. The former definition meets the classical placebo role in RCTs, but the latter acknowledges that it's rather impossible to separate the "placebo effect" from the real effect of a given drug or intervention. Furthermore, the placebo effect is built-in to any given treatment, even when no physical placebo is given.

EVIDENCE OF PLACEBO RESPONSE

A 2004 update on a systematic review found only limited evidence of clinical effects as a consequence of placebos, pointing out that they had possible benefits only in studies with continuous subjective pain outcomes[22]. Nevertheless, literature on significant placebo response is abundant.

In a classic experiment, medical students were told they would receive tablets with sedative or stimulant effects. All of them received either one or two blue or pink pills. However, every pill was placebo. It was found that "two capsules produced more effects than one, and blue capsules were more sedative than the pink ones"[23]. Commercial variables also affect expectations and influences therapeutic efficacy. When patients were given a famous pain killer in a branded or unbranded form with either an inert or an active formulation, Aspirin was more effective than placebo, and branded tablets (both active and placebo) were more effective than their unbranded counterparts[24]. Another study found that patients who were told their pills were more expensive (USD$2.50) had more symptomatic relief than those who were told their pills cost just 10 cents[25].

The placebo response may also be observed by increasing expectations about an intervention. In a study of the University of Connecticut[26], subjects were given decaffeinated coffee, with deceptive or double-blind instructions. One group was told they would receive regular coffee, and the other group was

told they would receive either regular or decaffeinated coffee. The first group had a greater increase in alertness, heart rate and blood pressure than the second group (and no one actually received caffeine!). Verbal suggestions can alter patient's expectations and lead to placebo effects. A patient can make use of a topical placebo cream with two different suggestions: that the cream is inert or that it is a powerful analgesic. The outcomes will surely be different[27].

Knowing that a treatment is being administered, also known as open-hidden paradigm, is one of the most evident findings supporting placebo effect in clinical care. Patients who could see the medication being administered experienced greater symptom relief than when treatment was given in a hidden manner, *i.e.*, without the patient's knowledge. Interestingly, in this case, no actual placebo has been given[28]. Practitioner's expectations are also shown to influence patient outcomes as well. In a RCT on dental pain, patients could either receive fentanyl, naloxone or placebo. This time the investigators were the ones deceived. In the initial phase of the study they were told patients would only receive naloxone (to increase pain) or placebo. In a second phase investigators were told that a fentanyl group (for analgesia) was included. Placebo in the first group led to less improvement than in the second group, meaning that investigator pessimism about proportion of patients receiving correct therapy could have negatively influenced the outcome[18].

PLACEBO RESPONSE IN OA

The placebo response is best documented for pain and distress, two main targets in patients with OA[20]. In a systematic review involving 16364 patients that received placebo in OA, RCTs confirmed that placebo response occurs in OA. Moreover, the overall ES for pain relief was 0.51, a very substantial number and greater than most specific effect obtained from any other individual treatment for OA[14]. In a randomized controlled trial of acupuncture for OA, traditional Chinese acupuncture was found not to be superior to sham acupuncture. However, "acupuncturists' styles had significant effects on pain reduction and satisfaction, suggesting that the analgesic benefits of acupuncture can be partially mediated through placebo effects related to the acupuncturist's behavior"[29]. Telephone contact is shown to be a useful intervention that can enhance the functional status of OA patients by reducing pain and improving psychological health[30]. Although patients may actually receive useful treatment information by phone, the call itself surely exerts a powerful placebo effect.

The method of delivery is also very important. In general, the more invasive and the more frequently administered an intervention the higher the placebo effect[14]. Bannuru *et al*[31] showed that some types of placebo interventions are associated with greater responses in patients with OA (intra-articular and topical placebo effects higher than oral). Thus, it is not surprising that sham arthroscopy of the knee has a very large placebo effect[32]. Even the way that practitioners interact with patient can be of influence. Contextual aspects, such as a warm, attentive, confident and optimistic consultation, as well as the patient's perception that the practitioner is competent and wishes to monitor his/her progress, may also positively influence the outcome. In a study by Thomas[33], all patients received thiamine tablets as placebo medication. A "positive" consultation, with confident diagnosis and reassuring attitude produced better outcomes than a "negative" consultation.

FINAL CONSIDERATIONS

Since the second half of the 20th century, the use of placebo has been loathed and, apart from the common use as a control in RCTs, it is sometimes used with negative purposes, like to determine if a patient is faking its symptoms. In light of recent publications, we need to have a better understanding about how the interactions between patients, physicians and context work. It is well proven that the placebo effect is real, especially in painful disorders like OA. However, with such a large and varied amount of available treatment modalities, it's obvious that we are not considering giving sugar pills or saline solutions when talking about the use of placebos in OA treatment. Moreover, it is neither acceptable nor ethical to prescribe more frequent and/or invasive treatments, or more expensive ones to achieve a placebo response.

The greatest impact that placebo effect can have on our practice is to give us new insights about patient care. Controversial treatment modalities such as insoles[34], viscosupplementation, mind-body therapies, physical therapies and chondroprotective drugs perhaps would not be controversial at all if the only evidence accepted didn't come from methods of evidence-based medicine that are currently very rigorous, with strict inclusion criteria, minimum follow-up requirement and the use of minimum clinically important improvement concept. It seems unrighteous, for example, to obtain statistically significant results favoring chondroprotective agents used as monotherapy and compared to a powerful placebo and consider it "not clinically relevant"[35].

We are far from treating effectively our OA patients. And the burden of the disease only grows, since population is aging. Maybe we should make more use of non-pharmacological tools and chondroprotective agents. Even in light of the current lack of "high level of evidence" data, we should give such tools more credit, and genuinely believe that they may help. In

a positive expectation environment, with a warm and reassuring consultation and a desire for follow-up, we can surely improve practitioner-patient relationship and be more effective. We certainly can use the placebo effect to our favor.

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REVIEW

Effect of bone loss in anterior shoulder instability

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Abstract

Anterior shoulder instability with bone loss can be a difficult problem to treat. It usually involves a component of either glenoid deficiency or a Hill-Sachs lesion. Recent data shows that soft tissue procedures alone are typically not adequate to provide stability to the shoulder. As such, numerous surgical procedures have been described to directly address these bony deficits. For glenoid defects, coracoid transfer and iliac crest bone block procedures are popular and effective. For humeral head defects, both remplissage and osteochondral allografts have decreased the rates of recurrent instability. Our review provides an overview of current literature addressing these treatment options and others for addressing bone loss complicating anterior glenohumeral instability.

Key words: Latarjet; Remplissage; Glenoid deficiency; Hill-Sachs lesion; Anterior instability

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Core tip: Anterior bony instability is a multifactorial problem, with osseous lesions existing on the glenoid, the humeral head or in combination. For glenoid lesions recent data has suggested Latarjet as a good option in these patients, with the potential in the near future for a technically feasible arthroscopic approach. With humeral head lesions, remplissage has demonstrated excellent short-term outcomes and offers an arthroscopic method. In the future longer-term studies will be needed for the remplissage procedure. Overall, there are many surgical options to treat these difficult patients each with their own unique aspects.

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INTRODUCTION

The incidence of shoulder instability in the population is estimated to be as high as 2%[1]. While many first-time dislocators can be managed conservatively, there are specific patient groups that have a higher risk for dislocation after a single event and may benefit from surgical stabilization. For example, Taylor *et al*[2] found increased risk of recurrence in overhead athletes and participants in contact sports. In addition, hyper-laxity has been an identified risk factor[3]. Of the risk

factors for recurrence, the most predictive is age at the time of first dislocation. Increasing instability risk has been found to be inversely proportional to the age of the patient[4]. For example, in older patients the risk of instability ranges from 10% to 20%[5]; yet in skeletally immature patients, Marans *et al*[6] found a re-dislocation rate of up to 100%. While demographics play a major role in anterior instability, intra-articular pathology also has a strong association.

The most difficult dislocators to treat are those with bony deficits. After first time anterior dislocation, glenohumeral deficiency (humeral head defect, glenoid defect or combination of both) has been found in up to 70% of patients[7]. While small defects tend to have limited implications on overall stability, there is a significantly increased risk of instability as the size of the humeral head lesion or glenoid deficiency increases[8,9]. Historically, these large defects had been treated with isolated soft tissue procedures, but further biomechanical and clinical studies have led to treatment algorithms that focus more on addressing the bone loss. Given these concerns, our purpose is to review recent data on surgical management of anterior instability with associated bone loss.

TYPES OF BONE LOSS

In bony anterior instability, both articulations of the glenohumeral joint have been associated with increased risk of further dislocations. Defects can occur on the glenoid side (*i.e.*, Bony Bankart lesions), on the humeral side (*i.e.*, Hill Sachs lesions), or on both sides.

Glenoid deficits

Glenoid deficiency has been found in up to 22% of patients after initial dislocation[10]. In recurrent instability cases their incidence ranges from 46% to 86%[11,12]. To understand the biomechanics of the glenoid deficiency, initial discussion should be begin with the discussion of small defects. First described by Dr. Arthur Bankart, these anterior labral lesions (known as Bankart lesions) increase the risk of instability. If a small piece of the anterior glenoid rim is concomitant with these labral tears some refer to this as "bony Bankart lesions. As the pieces become large the propensity for dislocation increases. As these defects approach greater than 20% to 25% of the glenoid the glenoid appearance changes. Burkhart *et al*[13] first described this glenoid appearance as an "inverted pear". His colleagues found in larger defects the standard pear shaped appearance of the glenoid was reversed. As a result the glenoid is wider superiorly than inferiorly, giving it an inverted pear appearance. When this occurs, they described a disruption in the arc of motion with abduction and external rotation of the arm, creating an increased risk of recurrent dislocation.

Gerber *et al*[14] confirmed this theory in their biomechanical study. They found with subsequent loss of anterior inferior glenoid arc the resistances to dislocation decreased exponentially (Figure 1). Newer biomechanical studies have further described this "glenoid track". This concept has shifted the previous paradigm from engaging defects to track-off track mismatch. Yamamoto *et al*[15] evaluated 9 cadaveric shoulders and found dislocation was most likely with disruption of the medial margin of this track.

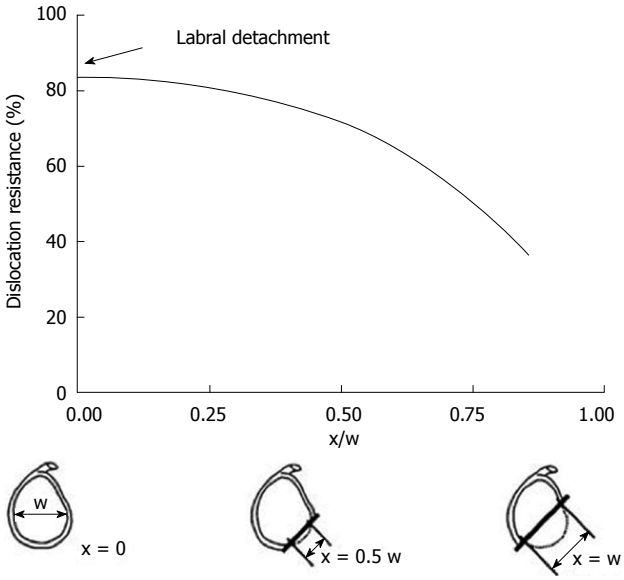

Figure 1 The graph demonstrates the relationship between the size of the glenoid rim and the dislocation risk. When defect (×) measure more than 50% of the glenoid width there is a significant drop in dislocation resistance. Adapted with permission from *Clin Orthop Related Res* 2002; **400**: 65-76.

While understanding the biomechanics of glenoid defects is necessary, Bigliani's classification of the glenoid deficit best defines clinical prognostic features[11]. He defined four types of glenoid defects: type 1 involves a non-displaced anterior glenoid fragment, type 2 is a small detached anterior fragment, and type 3a involves anterior glenoid deficits of < 25%, while type 3b involves defects greater than 25%. These distinctions determine the need for bony reconstruction. They recommended soft tissue procedures for types 1, 2, 3a while type 3b defects should have glenoid augmentation. Mologne *et al*[16] also recommend glenoid restoration for defects greater than 20% to 25% of the glenoid surface. They reached this conclusion after performing soft tissue repair on 23 patients with glenoid defects greater than 20% and had a 14% failure rate at 34 mo follow up when bony incorporation did not occur. An additional study by Burkhart *et al*[17], who performed 194 consecutive arthroscopic Bankart repairs and found in 18 patients with glenoid defects larger than 25% of the glenoid[17]. In this group they had a failure rate 67%, compared to the failure rate of patients without bony defects at 4%. As a result, they advocated for addressing the bony defects, as soft tissue repair alone did not provide

adequate stability.

These glenoid cutoffs have been further supported by other biomechanical studies. Itoi *et al*[18] evaluated 10 cadaveric shoulders and performed four separate glenoid osteotomies each with increasingly larger deficits. They found a significant decrease in stability with glenoid defects above 21%. Greis *et al*[19], who had similar study methods, reported significant increases in dislocation risk and contact pressures at more than 31% loss of the glenoid arc. Overall, these studies support that isolated soft tissue repair is likely insufficient in preventing recurrent instability in patients with large glenoid deficiencies.

Humeral head defects

While humeral head defects can be found concomitantly with glenoid pathology, isolated depressions can significantly affect the stability of the shoulder. These lesions have been found in up to 70% of first time dislocators[7], and up to 100% of patients with recurrent instability or after failed primary stabilization[7,10,20,21].

Hill and Sachs[22] first classified these lesions in 1940; as such they are frequently referred to as "Hill-Sachs lesions". In their landmark study they recognized these defects as markers for instability after an acute shoulder dislocation. These lesions were further defined by Boileau, who identified small to large Hill-Sachs lesions in up to 85% of their patients. They found significantly increased rates of recurrent instability in patients with these "Large" lesions[23]. In a retrospective case review by Burkhart and De Beers they explained that engagement into the glenoid rim was also needed for recurrent instability, and reported 100% recurrence in patients with an engaging Hill-Sachs[24]. As such this finding led them to suggest that if an engaging lesion is recognized, one must address not only the Bankart lesion but also take additional steps to treat the humeral head defect. In a follow up study, they further described this pattern of engagement, stating the Hill-Sachs lesion must be parallel to the arc of motion of the glenoid with abduction and external rotation to be truly engaging[17].

Despite previous clinical descriptions of size based on retrospective cases series, limited descriptions were available to define the percent of the humeral head defect necessary to cause recurrent instability. More recent biomechanical testing by Sekiya *et al*[25] demonstrated that humeral head lesions greater than 25% of the articular surface significantly increase the risk of recurrent instability. They recommended directly addressing the bony defect in these patients to prevent further instability. Additional studies have found ways to calculate this percent on MRI and CT scan to better define this distinct patient population[26,27].

Combined defects

While both Hill-Sachs lesions and glenoid defects each have an effect on the stability of the glenohumeral joint, combined lesion can add a level of complexity with regards to proper treatment selection. Indications for surgical management have been well described for isolated humeral head and glenoid defects. A recent study by Arceiro *et al*[28], evaluated the combined biomechanical effect of concomitant lesions. They developed their model using three-dimensional printing from CT scans of 142 patients, with varying degrees glenoid and Hill-Sachs lesions. After testing they found medium size Hill-Sachs lesion became clinically significant with greater than 2 mm of glenoid bone loss. Additionally with glenoid loss greater than 4 mm even small Hill-Sachs defects significantly increased instability despite a Bankart repair. As a result, they suggested bony augmentation with these combined defects. This understanding of the effects of these lesions on one another is essential, as soft tissue repair alone is likely not adequate in these clinical scenarios.

History

Clinical assessment of bony shoulder instability begins with a detailed history. Typically, an initial high-energy dislocation event occurs with the arm in an abducted, externally rotated, and extended position. These episodes often require reduction in the emergency room. Mechanisms involving an axial load on the glenoid predispose glenoid bone involvement[24]. Complaints of mechanical symptoms such as pain, crepitus, or catching when the arm is placed in the position of apprehension (abduction, external rotation) are suggestive of an engaging Hill-Sachs lesion. Subsequent instability in the midranges of motion (*e.g.*, 20 to 60 degrees of abduction)[29] or after lower energy events and with daily activities of living may suggest loss of bony constraints of the glenohumeral joint such as a large glenoid or humeral head defect[30-32]. Additionally, failed arthroscopic capsulolabral reconstructions or multiple recurrences within a short timeframe are suggestive of significant bony defects.

PHYSICAL EXAM

Both shoulders should be examined for evidence of muscular atrophy, deformities, active and passive range of motion, and evidence of prior surgeries. A careful neurovascular exam, including an accurate assessment of the axillary nerve should be performed, as axillary nerve injuries are commonly observed in the acute setting[33]. Assessment of the rotator cuff, with special attention to subscapularis function, should be performed particularly in patients who have undergone prior open stabilization because of potential for subscapularis repair failure. When performing provocative maneuvers, such as the apprehension test and relocation test, comparison to the contralateral shoulder is necessary to quantify the direction and magnitude of laxity. The load and shift test can identify the direction of instability as well as the adequacy of the glenoid concavity. To perform this test, a load is

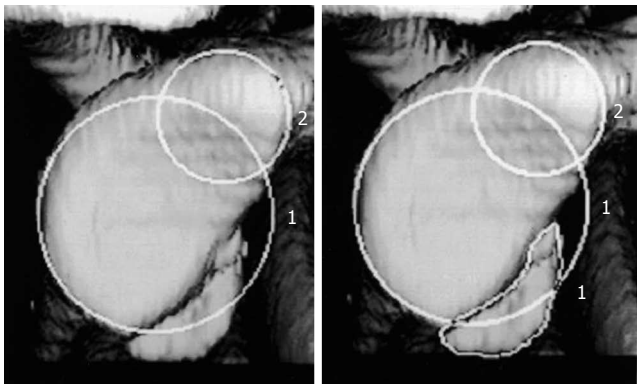

Figure 2 Using 3D reconstruction computed tomography the size o f the defect is calculated as the percentage of the on fossa glenoid. Using circle 2 as the reference selected by the radiologist, the CT software automatically calculates the deficit by using the equation (area of the deficit/circle 1 × 100%). Adapted with permission from *JBJS Am* 2003; **85-A**: 878-884.

placed on the humeral head to center it within the glenoid, and then a displacing force, either anterior or posterior, is applied to the humeral head. A decrease in resistance may be suggestive of a glenoid defect in the direction of displacement. The patient should also be asked to demonstrate the position of the shoulder at the time of initial dislocation or other subsequent events of instability or apprehension. Unlike patients with multidirectional instability, unidirectional and greater apprehension in the early and midrange of motion (*e.g*., 20 to 60 degrees) is also suggestive of more significant soft-tissue pathology and/or bony involvement[34,35].

IMAGING

While plain radiographs remain the mainstay of initial assessment, they are only moderately accurate at diagnosing bony defects[11,36]. Glenoid fragments may be visualized on standard AP or projects parallel to the glenoid such as an axillary or glenoid profile view[37]. Angled projects, such as the apical oblique[38] or Didiee[39], views have the highest yield in detecting glenoid defects on plain radiographs. The West Point view function similar to the Garth view but is designed to assess the anterior-inferior glenoid rim[40] and has demonstrated a high correlation with computed tomography (CT) in estimating glenoid bone loss[36]. Another view most commonly used in Europe is the Bergeneau view to assess anterior inferior bone loss. This view requires fluoroscopic imaging to get the perfect on fosse view as such its utility has been limited in the United States[41]. For humeral lesions, the Stryker notch or internal rotated AP views are more sensitive[39]. The Stryker notch, which can evaluate the size and orientation of a Hill-Sachs lesion[42], is obtained by placing the palm of the hand on top of the head, with fingers directed toward the back of the head. The beam is centered over the coracoid process and aimed 10 degrees cephalad.

CT with 3D reconstruction, however, remains the gold standard in the evaluation of bone deficiency[11]. The sagittal 3D reconstruction with digital subtraction of the humeral head has been recommended for the evaluation of glenoid deficiency[32,43,44]. Using this modality, the glenoid defect can be quantified. A best-fit circle drawn on the inferior two thirds of the glenoid and the amount of bone missing is determined as a percentage of the total surface area of the circle. This is calculated directly by CT scan software[26,45] (Figure 2). To assess humeral lesions, the defect arc on coronal or axial cuts can be divided by the humeral head arc to quantify Hill-Sachs lesions[46]. Magnetic resonance imaging (MRI) may be useful in evaluating glenoid rim defects, soft tissue lesions, and for quantifying humeral impaction fractures, but are generally thought to be less accurate than CT for bony assessment[27,47].

ARTHROSCOPY MEASUREMENTS

An evaluation and assessment of bony defects should be performed during the initial diagnostic arthroscopy. The bare area has been shown to reliable mark the center of the inferior glenoid[45,48,49]. Using the bare area as a landmark, a calibrated probe can used to measure the distance from the bare spot to the posterior rim and compare it to the distance from the anterior rim. Assuming that the normal inferior glenoid is shaped as a nearly perfect circle[45], anterior-inferior glenoid deficiencies can then be quantified by the following[50]:

Glenoid deficiency = (Distance from bare spot to posterior rim - Distance from bare spot to anterior rim)/(2 × Distance from bare area to posterior rim)

Quantification of glenoid bone loss should be routinely performed to determine the ideal anterior stabilization procedure (Figure 3).

OPEN *VS* ARTHROSCOPIC TECHNIQUES

With advancing technology, arthroscopic techniques are becoming more popular. For small defects or soft tissues avulsions, the results are fairly definitive. Recent studies have demonstrated similar recurrence rate and outcomes for arthroscopic techniques compared to open procedures in most patient populations[51]. A larger systematic review by Harris *et al*[52] evaluated longer-term outcomes of Bankart repairs from 26 studies and also found no statistical difference between open *vs* arthroscopic approaches[52].

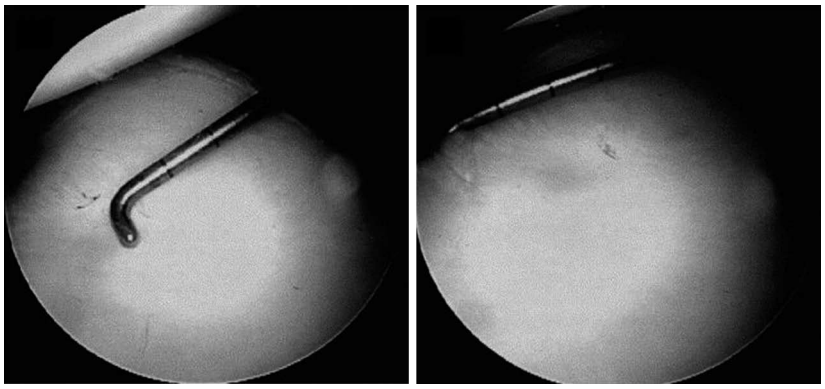

Figure 3 Through a posterior portal a 3 mm calibrate probe is inserted and the distance from the center of the bare spot to the posterior glenoid rim is measured. Following the distance from the bare sport to the anterior glenoid rim is measured. These values are used to preform the final glenoid deficit calculation. Adapted with permission from *Arthroscopy* 2004; **20**: 169-174.

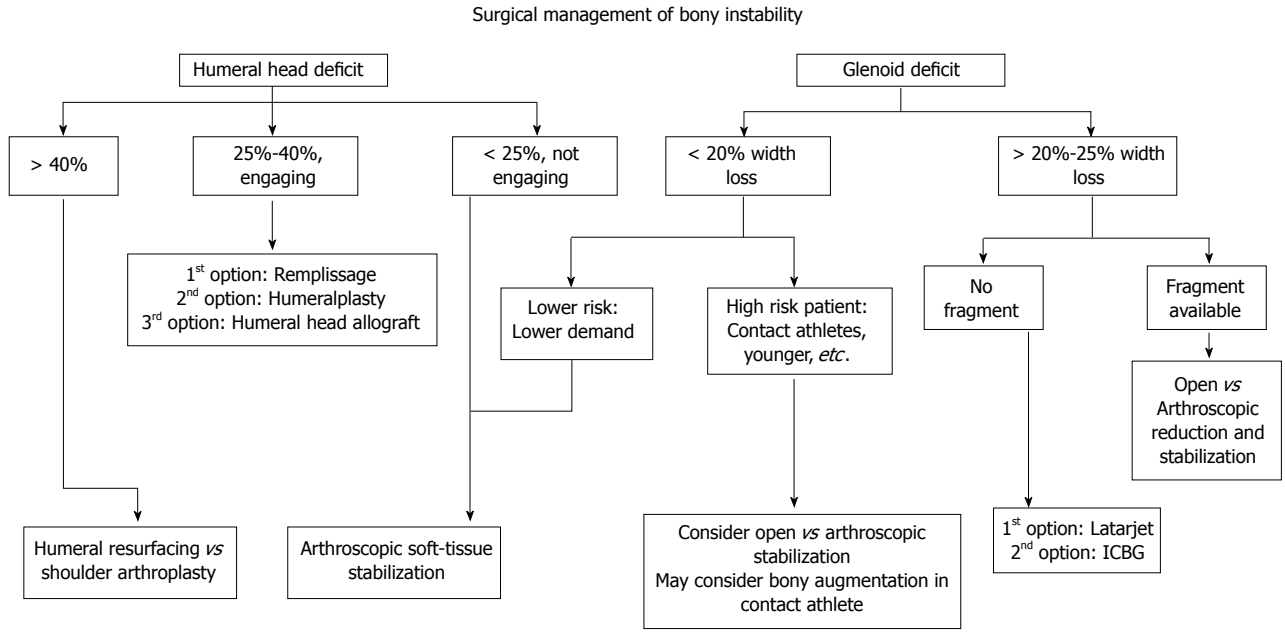

Figure 4 Our treatment algorithm of bony anterior shoulder stability. First determination of the size of the defect is done, followed by evaluation of specific risk factors. For large glenoid defects the Latarjet procedure is preferred, while Hill-Sachs defects the remplissage is our recommended procedure.

Despite this data most studies have failed to evaluate specific patient groups at higher risk. Burkhart *et al*[24] recommend open surgical management with younger patients, overhead or contact athletes. Another study by Rhee *et al*[4] found significantly higher recurrence rates after arthroscopic stabilization at 25% compared to open procedures at 13% in these contact athletes. As such they suggested open repair in these patients. In addition, a prospective study by Mohtadi *et al*[53] randomized 196 patients without identified bony lesions on radiographs to open *vs* arthroscopic repair. Additionally they matched patients by age (average age 27 years) and sex. They reported lower recurrence rates after open procedures at 11% compared to 23% for the arthroscopic stabilization group. While these are impressive results, they did have a trend towards more patients in the arthroscopic group who played a contact sport ($P < 0.09$). Finally a metanalysis by Chen *et al*[54] of 16 trials with 827 shoulders compared open to arthroscopic stabilization. They found arthroscopic approaches had significantly better post-operative range of motion, but reoperation rate (10.1% *vs* 3.5%; OR 2.63) and recurrence rate (13.1% *vs* 4.5%; OR 2.63) were significantly higher than open repair. While arthroscopic techniques are more commonly chosen for soft tissue instability, there has been a trend towards open stabilization for bony defects and certain high-risk groups.

SURGICAL MANAGEMENT

Glenoid defects

Large glenoid defects can be a difficult problem to manage (Figure 4). The initial consideration when determining the best treatment should include evaluation of the acuity of the glenoid injury. For acute lesions, Park *et al*[55] reported good results after direct repair of the fracture. For chronic injuries there is generally no fragment and bone loss must be reconstructed. We will review surgical techniques for these chronic glenoid defects.

The bristow procedure

Helfet first described the Bristow procedure in 1958. It involved transfer of the terminal 1 cm of the coracoid to the glenoid rim[56]. Usually the piece is secured with a single screw. The conjoined tendon is left intact to the transferred coracoid piece to act as a soft-tissue sling in abduction. Alternatively, detaching the tendinous attachments from the coracoid graft has been described, though we do not recommend this.

Hovelius *et al*[57] performed one of the largest studies of the Bristow procedure. He prospectively evaluated 319 patients with an average follow was 15.2 years and an overall satisfaction rate of 95%. For outcome scores, they reported 86% excellent to good Rowe scores and WOSI scores of 84.7%. Their recurrence rate was 20%, with 5% dislocation and 15% of patients with a postoperative subluxation. Additionally they found 14% of patients had mild arthropathy on radiographs, which directly correlated with lateral misplacement of the coracoid graft.

In the study by Schroder *et al*[58], the authors reported results of the Bristow procedure on 52 Navy midshipmen with 26 year follow up[58]. The failure rate was 15.4% with 9.6% dislocations and 5.8% subluxations. Sixty-nine percent of postoperative WOSI scores were good to excellent. They also found a significant loss in external rotation as well as an increased risk of glenohumeral arthritis in their cohort. Furthermore, 15% of the patients underwent a revision surgery on their shoulder.

Yamashita *et al*[59] evaluated 126 patients treated with concomitant Bankart repair and Bristow procedure. Their follow up was 41 mo, with a recurrence rate at 1.6%. For range of motion they reported an average loss of external rotation of 13 degrees.

While results have been promising for the Bristow procedure, longer-term studies have demonstrated increased risk of glenohumeral arthritis and external rotation loss as well as recurrence rates of up to 18%. These factors must be taken into account in treating this difficult patient population.

The latarjet procedure

Dr. Michel Latarjet described the Latarjet procedure four years before the Bristow procedure[60]. While studies have used term Latarjet-Bristow procedure synonymously, there are variable differences. Recently, the Latarjet has been the preferred technique because it uses a larger coracoid osteotomy of 2 to 3 cm. This increased length allows the surgeon to place the fragment more perpendicular to the base of the glenoid. Additionally, biomechanical evaluation has demonstrated improved stability with larger portions of the coracoid. Giles *et al*[61] evaluated 8 cadaveric shoulders comparing the stability of the Bristow to the Latarjet procedure. They found significantly more dislocations in the Bristow group with glenoid defects of 15% and 30% in comparison to the Latarjet procedure. As a result, they recommend the Latarjet procedure for these larger glenoid defects.

For surgical technique, a 1-cm cuff of coraco-acromial ligament (CAL) is left on the coracoid process (Figure 5). The coracoid is osteotomized at the "knee" (junction of horizontal and vertical parts), perpendicular to its base. All soft tissue is removed except the conjoined tendon and the CAL stump. Next the graft is molded with an oscillating saw to expose a broad flat cancellous bed to optimize healing. The coracoid is predrilled with 2 k-wire roughly 1 cm apart. The graft is passed through a split in the mid-portion of the subscapularis tendon and is then fixed 1-2 mm medial with the glenoid articular surface. This is done with two partially threaded screws, starting with the inferior screw. Following this the capsule is imbricated to the CAL stump with two sutures[62] (Figure 6).

A long-term study by Allain *et al*[63] evaluated 56 patients with an average follow up of 14.3 years who underwent the Latarjet procedure. For outcomes they reported 88% good to excellent Rowe scores. Their failure rate was 12% with no recurrent dislocations and 12% subluxations. As for range of motion, they had a significant loss of external rotation of 21 degrees. For longer-term evaluation, 65% of their patient developed glenohumeral arthritis. As a result they analyzed coracoid placement and deduced lateral overhang increased risk of arthritis while over medialization increased the risk of recurrent instability.

An additional study by Mizuno *et al*[64] evaluated 68 patients with an average follow up of 20 years. Their average postoperative Rowe scores were 89.0 with a documented failure rate of 5.9%. With regards to arthritis, 20% of the patients had signs of glenohumeral arthritis at most recent follow up. Their risk factors for arthritis included age, high demand sports and lateral placement of coracoid.

The largest combined series reported by Young *et al*[62] evaluates over 2000 patients treated with the open latarjet procedure. For outcomes, 76% of patients had good to excellent Rowe scores. Also, 83% of patients returned to their preinjury sports level after surgery. They reported a failure rate of 1%, with no significant loss of external rotation.

Burkhart *et al*[65] performed a modified latarjet procedure on 102 patients with an average follow up of 4.9 years. For outcomes scores, their average Constant scores were 94.4. They reported a failure rate of 4.9% with 4 dislocations and 1 subluxation. In addition, they did not have a significant loss of external rotation with an average loss of 5.1 degrees.

While most reported series of Latarjet are performed as an open procedure, LaFosse recently described an arthroscopic technique. Dumont *et al*[66] published these results on 62 patients who underwent arthroscopic Latarjet with an average follow up of 6.4 years. Their reported failure rate was 1.6%, with no dislocations and 1 subluxation. For outcome scores their average

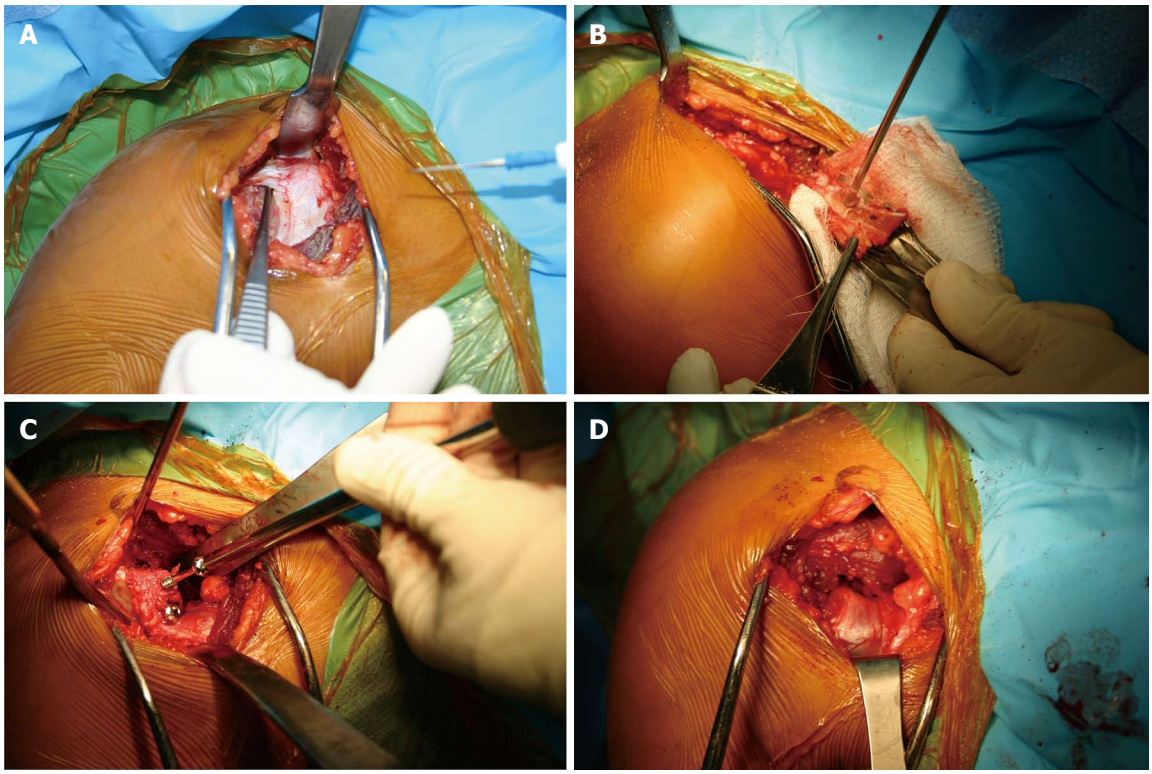

Figure 5 Intraoperative photos of the Latarjet technique. (A) Though a deltopectoral approach the coracoid is identified (B) after osteotomizing the coracoid the entry points for the 2 screws are predrilled, and the soft tissue attachments are preserved (C) The coracoid fragment is secured with 2 partially thread screws on the anterior surface of the glenoid (D) The joint capsule is secured to the coracoid fragment with 2 sutures.

WOSI score was 90.6. While these results are promising the arthroscopic approach can be technically demanding.

An additional arthroscopic study by Boileau *et al*[67] performed an arthroscopic Bristow-Latarjet procedure on 79 patients with a mean follow up of 35 mo. At final follow up, their average Rowe scores were 89.7 with a recurrence rate of 2%. For return to sport, 83% of patients returned to pre-injury level. They reported an average loss of 9 degrees of external rotation, with 73% of grafts demonstrating full healing at final follow up. They determined risk factors for non-union included age higher than 35 years old, smoking, or misplacement of screws. As such age and smoking should be taken into consideration before performing this procedure.

The Latarjet procedure offers a good option for large glenoid defects. Concerns about external rotation loss and long term arthritis still exist, though these may be minor in comparison to the reduced recurrent instability rates for this complicated patient population. An advance in techniques such as the arthroscopic methods has promise; though the learning curve needs to be improved before the full clinical application can be evaluated.

Eden-hybinette procedure

Similar to the Latarjet, the Eden-Hybinette procedure directly addresses large glenoid lesions. Hindmarsh first described this in 1967 using tibia autograft to reconstruct the glenoid track[68]. Recently this technique has been broadened to the use of iliac crest, femoral head, or osteochondral allograft to re-approximate the glenoid track[29,69,70]. Of these the most commonly used today is the iliac crest graft.

In this procedure, the curve of iliac wing is matched to that of the glenoid, with the concave inner table facing laterally. The graft is fixed such that the iliac wing natural contour roughly matches that of the glenoid articular arc. The cancellous base of the graft is secured to the glenoid neck with two screws. As opposed to the Latarjet, the capsule is attached anterior to the bone block, making the graft intra-articular (Figure 7).

Warner *et al*[29] performed this procedure on 11 patients with an average follow up of 33 mo. They reported no failures and at six month CT evaluation, all grafts had fully incorporated into the glenoid.

More recently, Scheibel *et al*[71] reported on 10 patients who underwent tricortical grafting. Their average follow up was 37.9 mo and reported no cases of recurrent instability. Average Constant scores were 88.3 and WOSI scores were 82.6. On further CT imaging they had full incorporation of all grafts and calculated that the glenoid track increased by an average of 18.4%. After examining radiographs, 30% of patients had signs of mild osteoarthritis.

A larger cohort by Auffarth *et al*[72] reviewed 47

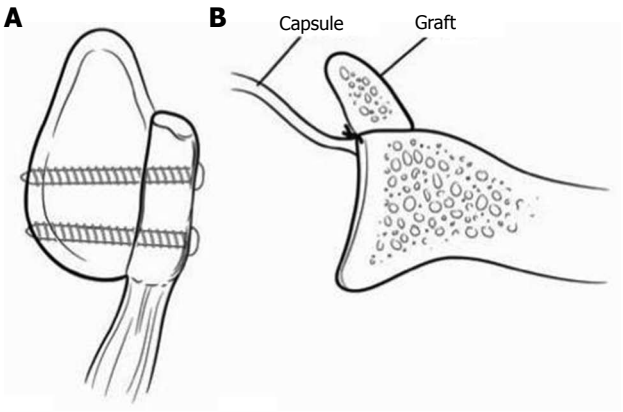

Figure 6 Represents a Latarjet procedure. A: A sagittal view with 2 screws securing the coracoid fragment; B: The capsule is secured posterior to the graft making the construct extra-articular. Adapted with permission from *J Am Acad Orthop Surg* 2009; **17**: 482-493.

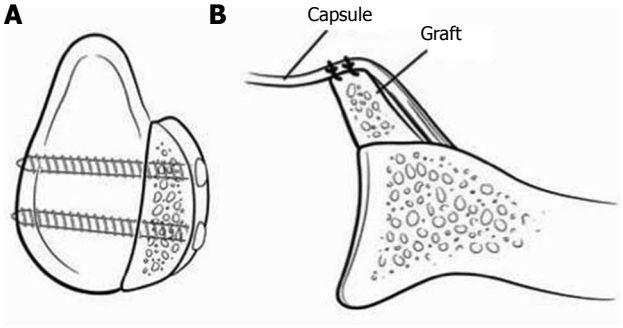

Figure 7 Represents an iliac crest autograft. A: A sagittal view with 2 screws securing the iliac crest; B: The capsule is placed anteriorly making the construct intra-articular. The graphs natural wing is facing towards the joint to better match the glenoid previous contour. Adapted with permission from *J Am Acad Orthop Surg* 2009; **17**: 482-493.

patients with an average Rowe score of 94.3 and no recurrent instability. Postoperatively, they had one traumatic graft failure and five iatrogenic nerve palsies at the donor site. In addition, long term data found 19.1% patients developed mild to moderate arthritis despite anatomic reduction.

Longer-term follow up Rahme *et al*[73] found more complications than previous studies. They reported results of 77 patients with a mean follow up of 29 years. Overall 83% of patients had good to excellent Rowe scores. Of concern they had a 20% recurrence rate. Furthermore, 50% of their patients developed glenohumeral arthritis and had a significant loss of external rotation. Additionally there were risks found associated with the use of autologous iliac crest graft, including hip pain and wound complications.

While these long-term results have limited the procedure's overall clinical use, recent reports by Lunn *et al*[74] found it to be an adequate alternative after failed Latarjet procedure. They performed the procedure on 46 patients after recurrent instability with a previous Latarjet procedure. They reported good to excellent results in 70% of patients with a 13.0% failure rate.

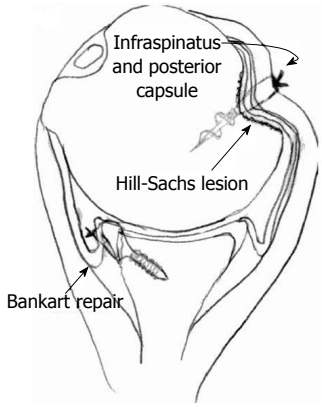

Figure 8 The remplissage technique with a suture anchor securing the infraspinatus and the posterior capsule into the Hill-Sachs defect. In addition, a Bankart repair is performed during the procedure. Adapted with permission from *Arthroscopy* 2008; **24**: 723-726.

As iliac crest bone graft has recently been the mainstay of allograft glenoid augmentation, additional studies have evaluated other sources for glenoid arc restoration. Provencher *et al*[69] used distal tibia allograft for glenoid deficiencies greater than 25%. In addition they reported biomechanical data stating constant pressure remained low in the implanted allograft with range of motion testing. In their cadavers, they showed the articular deformity reconstructed by the tibial allograft was nearly identical to the intact state. For patient results, they reported good results in a series of three patients with full incorporation of the graft on CT scan at final follow up. Despite good fusions, they did not report range of motion testing or recurrence rates.

Another source a graft used by Weng *et al*[70], was fresh frozen glenoid allograft. They performed the procedure on 9 patients with an average follow up of 4.5 years. All patients achieved bony union at 6 mo, with a mean loss of external rotation of 7 degrees. Despite some positive aspects of their study, they had a 22.2% recurrence rate. Given this high recurrence rate it's likely further studies are need to determine the true clinical application of this procedure.

Overall since the introduction of the Eden-Hybinette procedure, many modifications of the technique have been described. While iliac crest bone grafting has become the predominant technique it is not without complications. These must be taken in consideration, and in many cases stabilization of the glenoid deficiency is based on surgeon preference as well as training.

HUMERAL HEAD LESIONS

While many patients with recurrent instability have elements of both glenoid and humeral bone loss, the amount of deficiency of each directly impacts surgical outcomes. Even in combined cases of both

glenoid and humeral bone loss, patient with large Hill-Sachs lesions continued to have instability despite glenoid reconstruction[75]. These findings suggest the need to directly address these Hill-Sachs lesions. In most studies, humeral head procedures are usually reserved for patients with deficits of 25% to 40%[76]. Yet while size plays an important role, the position of the engagement with abduction and external rotation (generally posterior and superior on the humeral head) increases the risk of dislocation as well[77] (Figure 4).

The remplissage procedure

The remplissage technique has become more popular in recent years as one of the mainstay treatments for large engaging Hill-Sachs lesions. Originating from the French word "to fill", it has gained further attention because it can be done arthroscopically and is technically reproducible. Purchase and Wolf originally described it in 2007. The procedure involves arthroscopic tenodesis of the infraspinatus into the humeral head defect and usually is accompanied by a Bankart repair[78] (Figure 8).

Boileau *et al*[79] evaluated 47 patients treated with remplissage with a mean follow up of 24 mo. Overall they had a 2% recurrence rate and reported an average loss of external rotation of 9 degrees. As for return to sports, 90% of patients returned to their previous sport and 68% of patients returned to their previous level of sport.

An early study by Park *et al*[80] evaluated 20 patients at a mean follow up of 29.2 mo. Their average ASES scores were 92.5 and average WOSI scores were 72.7. They reported a recurrence rate of 15% but no range of motion testing was done. Interestingly, in their follow up study of MRIs on separate remplissage patients, they found infraspinatus integration into the humeral footprint at as early as 8 mo. They suggested this incorporation might increase the chances of longer-term success of the procedure[81]. In addition, they also reported range of motion testing with a mean external rotation loss of 5.2 degrees.

Wolf *et al*[82] published longer-term results on their original patient series[78]. They included 59 patients with up to 10-year follow-up. They found minimal complications and no significant loss of external rotation. Overall their recurrence rate at long term follow up was 4.4% and mean Rowe and Constant scores were 95.0. Despite long-term follow-up, no evaluation for signs of arthritis was done.

More recently, systematic reviews have further compiled recurrence risk after arthroscopic remplissage. Buza *et al*[83] demonstrated low recurrence rates of all eligible studies at 5.4%, with mean external rotation loss of 2.6 degrees. Additionally Rashid *et al*[84] found average remplissage recurrence rate at 4.2% though their overall average external rotation loss was higher at 11.3 degrees.

Overall most of the results demonstrate remplissage has a low recurrence rates, with minimal complications. Even though most studies found no significant loss in external rotation, the concerns are still present given previous case reports and cadaveric studies[85,86]. Additionally, in throwing athletes where less substantial loss of external rotation are tolerated, the implications of this procedure must be discussed extensively with the patient. Despite good short term results, longer term studies are needed to evaluate long term effects, with a focus on glenohumeral arthritis which has been found with the glenoid restoring procedures.

Osteochondral allograft transplantation

Osteochondral allograft has been used for many orthopedic articular procedures. While a majority of the focus has been knee literature, humeral head defects are another area it has proven beneficial. One of the first studies by Miniaci *et al*[87] treated 18 patients with Hill-Sachs lesions of greater than 25%. They used custom matched osteochondral allograft and reported good results with no recurrent instability. As a result they suggested the advantage of the technique is the anatomic reconstruction. Unfortunately there were other risks including: graft resportion, non-union and hardware failure.

Two further case reports by Chapovsky *et al*[88] and Nathan *et al*[89] reviewed two adolescent patients treated with osteochondral allograft reconstruction for large Hill-Sachs lesions. At final follow up, these patients had stable shoulders and no signs of recurrent instability.

A more recent article by Garcia *et al*[90], looked at outcomes of 19 patients treated with OATs for engaging large Hill-Sachs lesions with a mean follow up 32.1 mo. They reported average WOSI scores of 74.7 but a high recurrence rate of 31.5%. In addition to documenting results of osteochondral allograft, they matched 20 remplissage patients with similar preoperative Hill-Sachs lesions. They reported that remplissage patients had a 50% lower recurrence rate, and after controlling for confounding variables had significantly better WOSI scores. While they concluded OATs procedure is beneficial in this patient population they recommend performing the remplissage procedure for larger Hill-Sachs lesions.

Though limited studies are available osteochondral allograft transplantation is a reasonable alternative for large engaging Hill-Sachs lesions. Concern for graft-associated complications exist, as such further study is needed before true clinical success can be determined.

Humeralplasty

This procedure involves reducing the Hill-Sachs lesion through an anterior humeral window. In theory, by directly restoring the anatomy, this would obviate the need for potential failures such as lack of infraspinatus integration or osteochondral healing. With regards to biomechanics, two recent cadaveric studies have

described such reduction techniques. The first study by Sandmann *et al*[91] described a method using balloon humeralplasty to reduce 80% of the lesions. More recently Stachowicz *et al*[92] used a similar method of balloon humeralplasty with 99.3% reduction of their Hill-Sachs lesions. Despite their biomechanical success, these studies were done with most of the soft tissue removed making the clinical application less relatable.

Re *et al*[93] did one of the few clinical studies; using a bone tamp and an ACL guide to reduce their Hill-Sachs lesions. They performed this technique in 4 patients and reported 12-mo follow up. They had good results with no recurrent instability and no postoperative complications. Despite good reductions, some of these patients did require concomitant Latarjet procedure, making it difficult to discern which procedure improved stability.

A second study by Hart *et al*[94] performed humeralplasty in 5 patients with humeral head defects of 30%. Their minimum follow up was 18 mo, with 100% satisfaction at final follow up. They reported no recurrent instability or postoperative complications.

While humeralplasty seems to have the most potential for anatomic reconstruction, limited cases series are available. In addition, this procedure is technically demanding and requires an open approach. Future studies are needed to evaluated longer-term results and possibly develop a minimally invasive method before true clinical application can be considered.

Larger hill-sachs lesions and humeral replacement

Techniques for humeral head defects from 25% to 40% have been discussed. When humeral head lesions approach greater than 40%, humeral resurfacing or traditional hemiarthroplasty has been suggested. Limited studies have evaluated these patients. Pritchett *et al*[95] described shoulder replacement results in 4 patients with humeral head defects up to 70% from chronic instability. All patients had good ROWE scores, but overall of range of motion improvement was poor. Despite these results arthroplasty techniques have improved significantly since this study and new implants have shown better longevity. Given the difficulty of dealing with these massive humeral head lesions, replacement still remains the best alternative at this point in time.

CONCLUSION

Anterior bony instability is a difficult pathology to manage and is multifactorial. As previously discussed, glenoid reconstruction is needed for defects greater than 20% to 25%. Multiple studies have shown improving the glenoid arc with a bony reconstructions is significantly better than soft tissues repair alone. Various surgical treatment options exist such as coracoid transfer, tibial autograft, iliac crest autograft, or osteochondral allograft. Each procedure has its own set of complications but has demonstrated improved recurrence rates in this patient population.

Humeral head lesions have also been identified as a source of instability. Studies have demonstrated that lesion greater than 25%-30% of the humeral head surface require reconstruction. To address these Hill-Sachs lesions, soft tissue, osteochondral allograft or anatomic reduction have been described and demonstrated significant improvement in stability of the shoulder. As bony deficiency of the glenohumeral joint is a common and difficult pathology to treat, surgeons must decide the best treatment based on the individual patient.

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MINIREVIEWS

Neuromuscular control and rehabilitation of the unstable ankle

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Abstract

Lateral ankle sprain is a common orthopedic injury with a very high recurrence rate in athletes. After decades of research, it is still unclear what contributes to the high recurrence rate of ankle sprain, and what is the most effective intervention to reduce the incident of initial and recurrent injuries. In addition, clinicians often implement balance training as part of the rehabilitation protocol in hopes of enhancing the neuromuscular control and proprioception of the ankle joint. However, there is no consensus on whether the neuromuscular control and proprioception are compromised in unstable ankles. To reduce the prevalence of ankle sprains, the effectiveness of engaging balance training to enhance the neuromuscular control and proprioception of the ankle joint is also questionable.

Key words: Ankle; Proprioception; Neuromuscular control; Physical therapy; Rehabilitation

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Core tip: Lateral ankle sprain is a common orthopedic injury with a high recurrence rate. However, there is no consensus on whether neuromuscular control and proprioception are compromised in unstable ankles, and whether proprioception training can reduce initial and recurrent ankle injuries. The purpose of this review is to discuss the etiology and intervention of initial and recurrent ankle sprains, focusing on the role of neuromuscular control and proprioception at the ankle joint. This review can provide clinicians the knowledge of constructing better examination protocols and rehabilitation programs for individuals with the unstable ankle.

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INTRODUCTION

Ankle sprains are among the most common musculoskeletal injuries with an estimated 23000 accidents occur daily in the United States[1]. Ankle sprains constitute up to 45% in sports related injuries[2],and basketball players are more vulnerable to ankle sprains (41.1% prevalence) than other athletes[3]. The

terminology of "sprain" indicates that the structural integrity of the ligament, which functions as a joint stabilizer, has been compromised. For the ankle joint, the ligaments on the lateral portion of the ankle (especially the anterior talo-fibular ligament) are most vulnerable to injuries. Lateral ankle sprains are likely the result of a fast combined motion of ankle plantar flexion and inversion, and such motion can occur when an individual lands on an uneven surface with a single limb[4]. It was reported that lateral ankle sprain comprises up to 83% of ankle injuries[5].

After the initial ankle sprain, mechanical restraints (*e.g.,* injured ligaments, joint capsule), muscle strength, and/or neuromuscular control (*e.g.,* proprioception deficits) may be compromised at the ankle joint[6-18]. As the result, 73% of the individuals who had sprained their ankles before are likely to experience recurrent injuries[19]. Despite decades of research on ankle sprain, is it unclear if compromised neuromuscular control and proprioception of the ankle joint contributes to initial and/or recurrent ankle sprains. Moreover, it is also unclear if neuromuscular training is effective in reducing the incidents of initial and/or recurrent ankle injuries.

Proprioception is an important element of the neuromuscular control. With proper proprioception, one may be able to timely detect the speed and magnitude of perturbation and react with proper muscle activation and joint motion. It is inconclusive if subjects with ankle instability experience proprioception deficits, and there is no standard testing and training protocols for ankle proprioception. The aim of this review is to discuss neuromuscular control and proprioception of the ankle joint, their potential deficits in unstable ankles, and the effectiveness of incorporating neuromuscular control training as part of the rehabilitation program.

INITIAL ANKLE SPRAIN

The ankle (talocrural) joint stability is achieved by weight loading on the bony structures (osseous congruity), proper activation of active stabilizers (muscles and their tendons), and maintaining the integrity of passive stabilizers (ligaments and joint capsule). The ankle joint reaches a stable position (closed packed position) with maximal dorsiflexion, and it becomes more unstable (subject to greater inversion) with plantar flexion. At its most vulnerable position (plantar flexion with inversion) for lateral ankle sprain, the 3 lateral ligaments (anterior talo-fibular ligament, calcaneo-fibular ligament, and posterior talo-fibular ligament) play the primary stabilization role at the ankle joint[20]. As a passive stabilizer, one cannot voluntarily tighten the ligament. Although ligament strength could be enhanced through proper loading and exercise, strength improvement in ligaments is very limited[21].

Neuromuscular control encompasses both reflexes and voluntary muscle responses. For reflex responses, sudden muscle length changes and the speed of changes would be detected by the muscle spindles of those stretched muscles (*e.g.,* peroneal muscles) during a sudden ankle inversion perturbation. A short latency/loop response (spinal reflex) would be elicited with a result of muscle activation at the stretched muscle. Meanwhile, information from the muscle spindles would also travel up to the supraspinal center, processed, and then the action potential would travel back to the stretched muscles (*e.g.,* peroneal muscles, tibialis anterior) to elicit a long latency response. The short latency response is typically fast enough but not powerful enough to correct a fast and large perturbation. In contrast, the long latency response could be powerful enough but is too slow to prevent injuries. The differences between short and long latency responses was demonstrated by Konradsen *et al*[22] with 10 healthy volunteers participated in their study. Standing on a custom platform with a secret trap door underneath the examined ankle, the trap door was able to tilt 30° in the frontal plane and provide a sudden ankle inversion perturbation to the subject. They found the initial peroneal muscle reflex response started around 54 ms post stretch (short latency response), but the muscle activation was too week to correct the perturbation[22]. The subject was not able to generate enough peroneal force to evert the ankle back until 176 ms after stretch (long latency response), which is significantly later than the estimated time frame (less than 100 ms post stretch) when a ligament injury would occur.

Proprioceptive information includes the position sense and movement sense (kinesthesia) of a joint. The ascending information from muscles (muscle spindles), tendons (Golgi Tendon Organs), and other mechanoreceptors located in skin, capsule, and ligaments can be used by the central nervous system to construct meaningful voluntary movements or to correct perturbations[23]. However, the reaction time of the voluntary movement is similar or larger than the long latency reflex[23], therefore too slow to prevent ankle sprains. In summary, interventions (*e.g.,* balance training) aim to enhance neuromuscular control and proprioception of an intact ankle may not reduce the incidents of future ankle injuries.

RECURRENT ANKLE SPRAIN

Because lateral ligaments (especially the anterior talo-fibular ligament) of the ankle joint play the primary role in ankle stability[20], compromised ligaments integrity after the initial injury (*e.g.,* ligament sprain, tear) can contribute to recurrent injuries. After the initial injury, the reparative phase may last for 3-6 wk and the remodel phase may last for more than a year after the injury. Moreover, only 50% to 85% of subjects with a prior ankle sprain reported full recovery 3 years after the initial injury[24]. If an individual returns to the same activity level or sports prior to a full recovery, recurrent ankle sprains are almost

inevitable.

It is suggested that altered neuromuscular control due to peripheral proprioception changes of the ankle joint may contribute to the high recurrence rate of lateral ankle sprain[8,11,12,14-18,25]. After the initial injury, overstretched/loosened ligaments and joint capsule may hamper the function of those mechanoreceptors in those structures. Some researchers reported prolonged peroneal muscle reflex latency in injured ankles[26-28], and others reported ankle position sense deficits in passive testing[8,12,29,30] and active testing protocols[12,15,29]. Moreover, it is indicated that the result of position sense testing (active matching of passive positioning) can be used to predict future ankle injuries[14,31].

Despite the previously described evidence that indicates proprioception changes in unstable ankles, there are also many studies that contradict those findings. No peroneal reflex latency difference[32-34], no position sense difference[35-37], and no movement sense (kinesthesia) difference[10] was found between healthy and unstable ankles. In addition, some studies indicate that the condition of ankle position sense is not a good predictor for future ankle sprains[13,38]. Moreover, Witchalls *et al*[39] used the Active Movement Extent Discrimination Apparatus (AMEDA) to compare ankle position sense and its improvement potential between healthy subjects and individuals with chronic ankle instability. With the AMEDA, their subjects were tested in a standing position with normal weight bearing and active control of their ankle joints, therefore with a better clinical and functional significance. They found no position sense difference between the two groups at their initial testing, but the individuals with ankle instability improved their scores less than healthy controls after repeated testing. Although it is unclear if subjects with unstable ankles exhibit position sense or movement sense deficits after the initial injury, as discussion in the prior section, the integrity of ankle proprioception may not play an important role in ankle stability against large and fast perturbations. Even with intact ankle proprioception, the short latency response (stretch reflex) would be too weak and the long latency reflex and voluntary muscle activation would be too slow to combat large and fast perturbations.

REHABILITATION FOR ANKLE SPRAIN

After decades of research, it is still unclear on what training technique/rehabilitation protocol is most effective in reducing the incidents of initial ankle sprains and recurrent injuries. Because proper proprioceptive information is an important part of the overall neuromuscular control, one might consider restoring the compromised proprioception may improve ankle stability. In order to improve ankle proprioception, it is essential to increase the sensitivity of mechanoreceptors by tightening up ligaments and joint capsules (enhance joint proprioceptors) and/or increase muscle activation (enhance muscle spindles). Without surgically tightening up the stretched/loosened ligaments and joint capsule, increasing muscle activation to sensitize muscle spindles through alpha-gamma co-activation could be a reasonable approach. However, even with better/intact proprioception at the ankle joint, one still cannot generate enough muscle strength that is fast enough to combat large and fast perturbations such as landing on an uneven surface.

The impact of muscle strength on ankle stability is unclear. Muscle weakness was reported in peroneal muscles[15,40,41], ankle dorsiflexors[38], and hip abductors[42] in individuals with ankle instability. However, other studies found no association between muscle weakness and ankle instability[14,37,43,44]. Although larger muscle activation can enhance the sensitivity of muscle spindles, strength training is not likely to reduce the incidents of initial and recurrent ankle sprains through enhancing neuromuscular control of the ankle joint. Instead, strength training may restore ankle muscle balance, position the ankle in more stable position (*e.g.,* more dorsiflexion with a stronger tibialis anterior), increase the strength of ligaments, and a larger/stronger muscle can also provide additional passive restraints to the ankle joint. Further research is needed to examine the impact of strength training on ankle stability.

Balance/postural training is the most commonly employed rehabilitation treatment for individuals with ankle instability. The majority of the literature reports positive therapeutic effects of balance training (*e.g.,* single limb standing, standing on an ankle disc/wobble board)[29,45-55]. However, there are a few studies that disagree with its treatment effect[56,57]. In the "Clinical Practice Guidelines" published in the *Journal of Orthopaedic and Sports Physical Therapy*, a panel of experts also concluded that the evidence is weak (grade of recommendation "C") on implementing weight-bearing functional exercises and balance activities on unstable surfaces[18]. If balance training is beneficial in reducing the incidents of ankle sprains, it is not likely due to enhanced neuromuscular control, but due to enhanced strength and stiffness in both muscles and ligaments at the ankle joint.

CONCLUSION

Initial and recurrent ankle sprains are a serious problem for athletes. After decades of research, there is still no consensus on the most effect intervention to reduce the incidents of initial and recurrent ankle sprains. Although passive ankle stabilizers such as ligaments provide the primary stability to the ankle joint, one cannot actively control the ligaments and their strength increment potential is limited. On the other hand, neuromuscular training has the potential to improve the latency and magnitude of muscle response of the long latency reflex and voluntary muscle activation. Such "reactive" responses can be

sped up slightly through neuromuscular training, but it is very unlikely to be fast enough to prevent injuries caused by a fast and large perturbation such as landing on an uneven surface with a single limb.

Balance training, neuromuscular training, and proprioception training are just a few terminologies that clinicians often use interchangeably to describe balance activities such as single leg standing and standing on an uneven surface such as a wobble board. It is important to know that improving neuromuscular control and proprioception of an ankle joint may yield little benefits in improving ankle stability against large and fast perturbations. However, balance training can also increase the strength of muscles and ligaments around the ankle joint. Since ligaments are the primary stabilizer of the ankle joint, treatment protocols with a balance training component may benefit the subjects with unstable ankles.

If a healthy ankle could not resist the fast and large perturbation during the initial injury, those compromised structures after an ankle sprain certainly would not be able to resist the same amount of stress without a full recovery. Most athletes did not wait for a year or longer (towards the end of the remodeling phase) before returning to their prior sports/activities. Therefore, it would be extremely difficult to reduce the incidents of recurrent ankle sprains in athletes.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Variability of platelet aggregation in patients with clopidogrel treatment and hip fracture: A retrospective case-control study on 112 patients

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Author contributions: Clareus A collected data and wrote the manuscript; Fredriksson I interpreted the MEA analyses and wrote the manuscript; Wallén H initiated the study, interpreted the MEA analyses and wrote the manuscript; Stark A operated patients and wrote the manuscript; Gordon M operated patients, performed the statistical analysis and wrote the manuscript; Sköldenberg O initiated the study, performed the statistical analysis, operated patients, supervised Clareus A and wrote the manuscript.
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Data sharing: Technical appendix, statistical code, and available from the corresponding author at olof.skoldenberg@ki.se. The presented data are anonymized and risk of identification is negligible.
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Abstract

AIM: To identify the rate of non-responders to clopidogrel treatment in hip fracture patients and study how non-responders differ from controls.

METHODS: In a retrospective case-control study we included 28 cases of acute proximal femoral fracture with clopidogrel treatment 2011 to 2013. Eighty-four controls from the same time period were included. Data collected included response to clopidogrel measured with multiple electrode aggregometry (MEA), intraoperative bleeding, erythrocyte transfusion, time to surgery and the incidence of adverse events up to 3 mo after surgery.

RESULTS: Eight (29%) of the 28 cases were non-responders. The median intraoperative bleeding was 300 mL (range, 0-1500), and was lower for non-responders (50 mL) but did not reach statistical significance. Erythrocyte transfusions did not differ between responders, non-responders and controls. Forty-five (40%) of 112 patients had adverse events postoperatively but the rate did not differ between patients with and without clopidogrel treatment.

CONCLUSION: Almost one-third of patients with

clopidogrel treatment and an acute proximal femoral fracture are non-responders to antiplatelet therapy and can be operated without delay.

Key words: Proximal femoral fracture; Clopidogrel; Variability; Bleeding; Adverse events

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Core tip: In this pilot study, almost one-third of patients with clopidogrel treatment and an acute proximal femoral fracture are non-responders to antiplatelet therapy. Analysis of variability in platelet aggregation can be used when fast tracking patients and we recommend this for emergency hospitals treating patients with acute proximal femoral fractures.

Clareus A, Fredriksson I, Wallén H, Gordon M, Stark A, Sköldenberg O. Variability of platelet aggregation in patients with clopidogrel treatment and hip fracture: A retrospective case-control study on 112 patients. *World J Orthop* 2015; 6(5): 439-445 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i5/439.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i5.439

INTRODUCTION

An increasing number of elderly patients are managed with long term antiplatelet therapy after cardiovascular and cerebrovascular events[1]. Clopidogrel is a frequently used antiplatelet drug which irreversibly inhibits ADP-induced platelet aggregation through blockade of the platelet P2Y12 receptor. Although the drug has been shown to be very effective in large clinical trials, there is a considerable inter-individual response to this drug. Depending on the platelet function method used and cut-off values set, between 5%-44% of patients have been shown to have reduced platelet inhibiting effect of the drug. The reason for this variability is likely multifactorial and include, *e.g.*, genotype, drug interactions and compliance to drug treatment[2-4].

Approximately 1 in 5 of patients with clopidogrel treatment will need non-cardiac surgery within two years[5]. It is well known that patients with clopidogrel treatment undergoing cardiovascular surgery have an increased risk of bleeding events during and after surgery. They also have a higher percentage of post-operative hemorrhagic complications and transfusions[6,7]. Clinical guidelines recommend that patients on clopidogrel treatment should interrupt their therapy 5-7 d before surgery to avoid increased intraoperative bleeding, even though recent studies of patients undergoing hip fracture surgery is inconsistent if the risk of perioperative bleeding is increased or not[8].

Patients suffering a hip fracture are elderly, and because of multiple co-morbidities attributed to age, they are one of the most fragile patient-groups in orthopedics, with a high morbidity and mortality following surgical treatment. Delayed surgery is associated with both increased frequency of medical complications and increased mortality[9,10]. Thus, the demand for rapid surgery is, for hip fracture patients with simultaneous clopidogrel treatment, contrasted against the bleeding risk for these patients.

Laboratory tests have recently been developed in order to examine platelet function bedside. One of these methods is multiple electrode aggregometry (MEA)[11]. This method can be used to assess platelet aggregation during treatment with platelet inhibiting agents such as clopidogrel, aspirin and other new platelet inhibitors in a venous whole blood sample (Figure 1)[11].

The rate of non-responders and responders for clopidogrel treated patients in hip fracture patients has, to the best of our knowledge, not been published in peer-reviewed literature. The aim of this study was to identify the rate of non-responders to clopidogrel treatment in hip fracture patients and to study if responders and non-responders differ from patients without clopidogrel in intraoperative bleeding and adverse events.

MATERIALS AND METHODS

Study design and setting

The study was conducted in accordance with the ethical principles of the Helsinki declaration and was approved by Ethics Committee of the Karolinska Institute. This retrospective case-control study was performed at the Orthopedic Department of Danderyd Hospital in collaboration with the Karolinska Institute (Department of Clinical Sciences at Danderyd Hospital) in Stockholm, Sweden. Danderyd Hospital is 1 of the 5 major emergency hospitals in Stockholm, providing medical care with a catchment area of approximately 500000 inhabitants.

Study subjects

At our department, we fast-track hip fracture patients and operate > 80% of patients within 24 h from arrival to the hospital[12]. We included patients undergoing treatment with clopidogrel who had a concomitant primary hip fracture or periprosthetic fracture that required acute surgery between 2011-2013. From this group, we excluded patients with non-displaced femoral neck fracture who underwent percutaneous internal fixation with cannulated screws because of the minimal risk of bleeding through this type of surgery. We also excluded patients with other acute orthopedic injuries and patients planned for elective surgery. Three matched controls for every included patient were identified from our department including all patients who had been treated at the clinic for hip fracture during 2010-2013. Patients with warfarin treatment were excluded from the control group. The controls

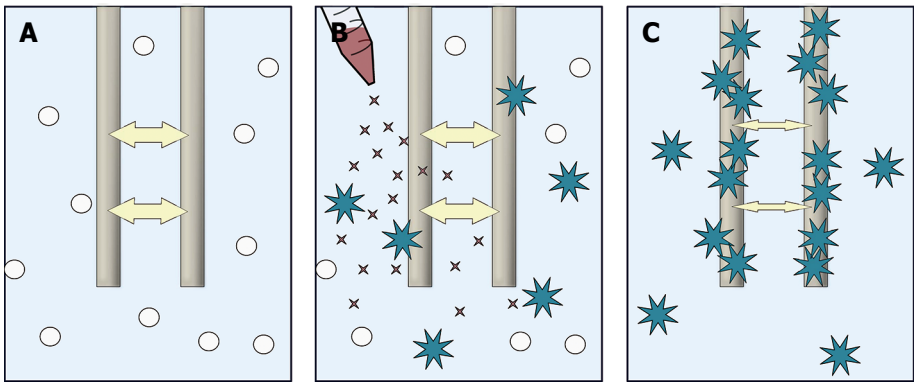

Figure 1 Schematic illustration of multiple electrode aggregometry. A: Whole blood sample is put in a twin impedance sensor; B: Addition of a platelet agonist activates platelets to adhere to the electrodes; C: When platelets adhere to electrodes there will be an increase in electrical resistance between electrodes. Electrical resistance is measured as a value of platelet activity. Platelets affected by clopidogrel treatment adhere less to electrodes.

were then matched according to age, type of fracture (inter- or subtrochanteric/femoral neck/periprosthetic), type of surgery (sliding hip screw or intramedullary nail/hip arthroplasty/plate osteosynthesis/femoral stem revision) and operation time.

Variables and data sources

The outcome variables were the rate of non-responders in patients with clopidogrel treatment, perioperative bleeding in millilitre and the occurrence of adverse events up to 3 mo after surgery. Other variables collected included sex, age, American Society of Anesthesiologists (ASA)-classification[13], type of surgery, type of fracture and surgery time.

Multiple electrode aggregometry

Blood samples for MEA were taken from an antecubital vein and collected in hirudin tubes (Refludan, Dynabyte). Test tubes were kept at room temperature until analysis 30-179 min after collection. MEA measured by Multiplate™ (Dynabyte, Munich, Germany) has been described elsewhere[14]. In brief, 300 μL of whole-blood is diluted 1:1 with 0.9% NaCl solution in cuvettes and heated to 37 ℃ under stirring for 3 min. After addition of a platelet agonist, platelets adhere to and aggregate on two pairs of silver-coated copper electrodes. The increase in electrical impedance between electrodes due to platelet aggregation is recorded in arbitrary units (AU) during 6 min (Figure 1). The MEA-value is the average area under the curve (AUC) for the two electrode pairs (AU*min) in the cuvette. For each patient 2 cuvettes were used. Adenosine diphosphate (ADP) was added at a final concentration of 6.4 μmol/L in each cuvette. We used the previously established cut off value to define clopidogrel responders[15]. Thus, responders were those who had a mean MEA ADP value of the readings obtained in the two cuvettes below 47 AU*min; non-responders were those with a value above this level[15].

Patient data

From digital patient records the following parameters were collected: Type of hip fracture, ASA grade[13], indication for clopidogrel treatment, time to surgery in hours (arrival at the emergency department to skin incision), choice of anesthesia (general/spinal), method of surgery, preoperative treatment with platelet transfusion, intraoperative bleeding (assessed from suctions, drainage and swabs used during surgery) and peri- and post-operative transfusion with erythrocyte units and plasma. The intra-operative blood loss was calculated by measuring the fluid in collection containers subtracting the amount of lavage and by weighing surgical swabs. The total amount of transfusions given with platelets, erythrocytes and fresh-frozen plasma was recorded. The occurrence of adverse events (AEs) was recorded. The World Health Organization (WHO) definitions were used. An AE is defined as any unfavourable or unintended sign, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure[16]. The Swedish personal identity number in conjunction with the Swedish Death Register and electronic hospital records was used to identify and verify all AEs as well as mortality up to 3 mo postoperatively.

Statistical analysis

Descriptive statistics were used. ANOVA and chi-square test were used to compare the groups. Bonferroni correction was used to correct for multiple comparison. The study size was derived from the number of available responders and non-responders during the study period. A P-value < 0.05 was considered significant. The statistical analysis was performed using SPSS Statistics software 22.0 for Mac (SPSS Inc., Chicago, IL).

RESULTS

Participants and descriptive data

One hundred and twelve patients were included in the study, 28 patients undergoing treatment with

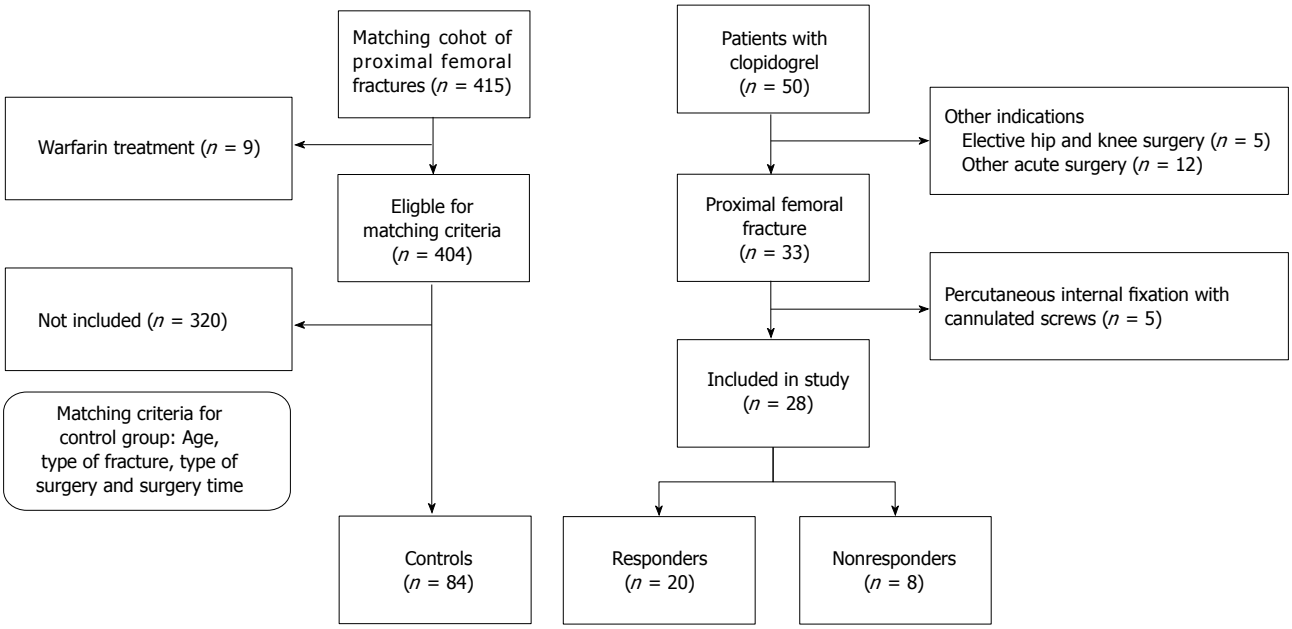

Figure 2 Flow of patients in the study.

Table 1 Cohort characteristics by treatment group *n* (%)

Variable	None (*n* = 84)	Responder (*n* = 20)	Non-responder (*n* = 8)
Sex			
Male	22 (26)	9 (45)	5 (62)
Female	62 (74)	11 (55)	3 (38)
Age	85 (± 7)	82 (± 9)	88 (± 4)
ASA class			
1-2	27 (32)	1 (5)	0 (0)
3-4	57 (68)	19 (95)	8 (100)
Fracture type			
Femoral neck	23 (27)	8 (40)	0 (0)
Per/subthrochanteric	46 (55)	8 (40)	7 (88)
Periprostethic	15 (18)	4 (20)	1 (12)
Surgery			
Hemi/total arthroplasty	23 (27)	8 (40)	0 (0)
Sliding hips screw or intramedullary nail	46 (55)	8 (40)	7 (88)
Locking plate osteosynthesis	6 (7)	1 (5)	1 (12)
Revision of implants	9 (11)	3 (15)	0 (0)

For continuous values the mean together with the standard deviation is used. ASA: American Society of Anesthesiologists.

clopidogrel and 84 controls [male/females: 36/76, mean age 84 (range, 56-99) years] (Figure 2, Table 1). 20 patients where under clopidogrel treatment because of cerebral insult, 6 because of myocardial infarction with following artery stenting, and in 2 cases the indication of clopidogrel treatment could not be found in referral. Nineteen (17%) of the patients died during the study, mortality rate did not differ between the groups.

Twenty of the patients with clopidogrel treatment showed results of MEA as responders to the drug and 8 (29%) patients were non-responders. The median intraoperative bleeding was 300 mL (range, 0-1800). The bleeding was lower for non-responders but this did not reach statistical significance (P = 0.8). The responder group did not have more intraoperative bleeding than controls (Table 2). We found no significant difference in erythrocyte transfusion between the groups, with a median number of 2 units for controls and non-responders and 1 unit for responders (Table 2). The anaesthesia, plasma and platelet transfusions given differed between the groups (Table 3). Although tranexamic acid was given to the majority of all patients, platelet and plasma transfusions were more frequently given to patients with clopidogreal treatment, especially the responder group. Notably, platelet transfusion was mainly given to those of the patients with the most pronounced platelet inhibiting effect of clopidogrel. In contrast, in the non-responder group transfusion was given to 1 of the 8 patients (Table 3). The mean (SD) time to surgery was 26 ± 19 h and differed between the groups (P = 0.001). Responders waited on average almost one day more for their surgery compared to the controls and non-responders (Table 2). In 7 patients in the responder group, the reason for prolonged time to surgery was pronounced effect of clopidogrel treatment with significanty lower values than the other responders. In these cases the risk of major bleeding was considered higher than the risk of delayed hip fracture surgery, and it was recommended from the cardiologist or anesthesiologist consulted to wait with surgery if possible. These patients were re-tested before surgery with multiple electrode aggregometry. Data showed that the antiplatelet effect of clopidogrel had decreased to a ADP value of over 47 (*i.e.,* a non-reponder value).

DISCUSSION

In this retrospective case-control study on patients

Table 2 Bleeding, erythrocyte transfusions and adverse events up to 3 mo follow-up

Variable	Control (*n* = 84)	Responder (*n* = 20)	Non-responder (*n* = 8)	*P*-value
Peroperative bleedning (mean ± SD)	350 (0-1800)	300 (50-1500)	150 (50-550)	0.8[2]
Any erythrocyte transfusion, *n* (%)	54 (64)	13 (65)	6 (75)	
Number of transfusions, median (range)	2 (0-10)	1 (0-6)	2 (0-6)	1.0[2]
Time to surgery (h), mean ± SD	21 (± 12)	45 (± 26)	28 (± 33)	0.003[2]
Adverse events				
Any AE, *n* (%)	31 (37)	9 (45)	5 (62)	1.0[3]
Type of AE, *n*[1]				
Deceased, *n*	14	2	3	
Hip related	6	2	0	
Cardiovascular	8	1	3	
Infection	14	9	4	
Other	24	6	3	

[1]Several patients had more than 1 AE; [2]ANOVA; [3]χ^2 test. Bonferroni correction has been applied to all *P*-values.

Table 3 Anaesthesia and transfusions *n* (%)

Variable	Control (*n* = 84)	Responder (*n* = 20)	Non-responder (*n* = 8)	*P*-value
Anaesthesia				
Spinal	82 (98)	5 (25)	7 (88)	1
General	2 (2)	15 (75)	1 (12)	
Tranexamic acid				
No	9 (11)	3 (15)	0 (0)	
Yes	75 (89)	17 (85)	8 (100)	0.003
Plasma transfusion transfusion				
No	83 (99)	15 (75)	7 (88)	
Yes	1 (1)	5 (25)	1 (12)	0.003
Thrombocyte transfusion				
No	84 (100)	9 (45)	7 (88)	
Yes	0 (0)	11 (55)	1 (12)	0.003

P-value derived from χ^2 test. Bonferroni correction has been applied to all *P*-values.

with a proximal femoral fracture and concurrent clopidogrel treatment almost one third of patients with clopidogrel were non-responders, indicating that they had no effect of this treatment, or that they were not compliant to medication. Thus, the incidence of non-responsiveness is similar to what we found in patients with ischemic stroke or TIA treated with clopidogrel at our institution[17]. By continuously using MEA at our department, we were able to fast-track non-responders to surgery within the same time as the control group (Table 2).

In previous publications, anti-platelet treated hip fracture patients have been delayed to surgery, often with negative effects on complication rate and mortality. Harty *et al*[18] included 21 patients on clopidogrel with acute hip fracture in a case-control study and found that patients on clopidogrel in mean waited 7 d for surgery, and 30-d mortality for these patients were 29%, compared to the control group who had surgery within 2 d and had a 30-d mortality of 4%. The authors conclude that surgery should not be postponed. A high rate of complications due to prolonged time to surgery was also observed in a study made of Johansen *et al*[19], where clopidogrel treated patients who waited 5 d for surgery had a higher rate of complications and they also found an increased intraoperative bleeding for patients who had surgery immediately. This result is in line with Chechik *et al*[20] study of 44 patients where clopidogrel was continued throughout surgery. In contrast to these findings, there are reports that have failed to find a difference in bleeding and complication rate between patients on clopidogrel and controls[21,22]. These inconsistences between existing studies is possibly, as in our study, due to the fact that a large proportion of patients are non-responders[23,24]. These relatively recent studies of hip fracture patients with clopidogrel treatment have not considered the individual responsiveness to the drug, which may be an important reason for the inconsistency in their results[18,20-22]. If almost one third of the patients with clopidogrel (as in our study) have no effect of treatment the non-responders could even out the results a group level and hide the actual bleeding risk for responders. More research is needed in this area but clearly observational and interventional studies on hip fracture patients with concurrent antiplatelet therapy need to take this into consideration for bleeding endpoints.

The clinical recommendation to discontinue clopidogrel treatment 5-7 d ahead of surgery is based on studies made for cardiological interventions. They have reported that continuation, or late (*i.e.*, 1 d) discontinuation of clopidogrel treatment is associated with increased intra- and postoperative bleeding and increased need for transfusions after coronary bypass surgery, compared to earlier discontinuation (*i.e.*, 3-5 d)[6,7,25]. For hip fracture patients, this discontinuation is in stark contrast to the need for rapid surgery. Delayed surgery is associated with both increased morbidity and mortality[12,26]. Both the 30-d all-cause mortality as well as minor and major medical complications are significant higher in hip fracture patients with surgical delay over 48 h[9,10].

When patients with increased risk of bleeding are identified, preoperative treatment can be customized. In the above mentioned studies of hip fracture surgery and clopidogrel treatment, it is not reported if preoperative treatment differ between clopidogrel

treated patients and controls. Wallace and Hossain report that all patients were medically optimized before surgery but do not mention if preoperative transfusion with platelets were given[22,27]. In our study patients with pronounced effect of the drug received platelet transfusions to higher extent than controls and those patients with none or low effect, and intraoperative bleeding did not differ between the groups. Neither did post-operative erythrocyte transfusion differ between the groups. Platelet transfusions should be administered with care, as whole blood transfusions, due to transfusion related complications such as infections, allergic reactions and febrile non-heamolytic transfusion[28]. This is why we find it important to identify patients that are at high risk for bleeding, so that we do not treat patients with platelet transfusion preoperatively if not needed.

In our study, non-responders were operated within the same time as controls, which likely reduces the risk of complications caused by delayed surgery. Patients with good response to the drug could either be optimized with platelet transfusion and operated immediately, or if their medical condition allowed, wait for surgery until a second analysis showed regression of clopidogrel effect. This is the reason why responders wait for surgery in mean 45 h compared to non-responders and controls who have surgery approximately within a day.

Analysis of platelet aggregation variability was also for help when planning for anaesthetics. Regional anaesthetics is associated with less risk for the patient compared to general anaesthetics and shortens operation time[29,30]. Hossain *et al*[27] reported in their study of 50 hip fractures and clopidogrel treatment that 88% of the patients had surgery in general anaesthesia, compared to controls were only 6% had general anaesthesia. In our study, patients eligible for spinal anaesthesia despite anti-platelet therapy could be identified preoperatively.

Variability of platelet function was, in the present study, evaluated with the MEA method. It is a standardized method to determine platelet function with high sensitivity and reproducibility[11]. The analysis is, compared to many other platelet function methods, a simple and rapid assay that can be used bedside in every day clinical practice. No centrifugation step which may influence platelet function is needed, as the analysis is made in a whole blood sample. Compared to template bleeding time which has previously been used to assess the risk of increased bleeding, the risk for user dependent variation is low since the method is easier to perform[11,14,31,32].

This is, to the best of our knowledge, the first published study where analysis of variability in platelet aggregation is used for patients with an acute proximal femoral fracture. We were able to obtain sound data on all studied outcome variable and found well matched controls for our cases. The main limitations of the study are the small sample size, retrospective design and relatively short follow-up. Thus, even though our groups did not differ in the incidence of adverse events or mortality rate, the study is not sufficiently powered for these outcomes. We have used intraoperative bleeding as a proxy for this, and most surgeons would agree that it is important to minimize blood loss for hip fracture patients. The study is also limited by intervention bias; MEA test was used to make clinical decisions such as platelet transfusions and surgical timing. These interventions could clearly have an effect on the results such as intraoperative bleeding as well as outcomes and differences between groups. This is however inherent in the method when using MEA and we believe that it is therefore this analysis is helpful for clinicians when making decision on timing of surgery.

In this pilot study, almost one-third of patients with clopidogrel treatment and a acute proximal femoral fracture are non-responders to antiplatelet therapy when presenting at the hospital. Analysis of variability in platelet aggregation can be used when fast tracking patients and we recommend this for emergency hospitals treating patients with acute proximal femoral fractures.

COMMENTS

Background

To identify the rate of non-responders to clopidogrel treatment in hip fracture patients and study how non-responders differ from controls.

Research frontiers

The incidence of non-responsiveness to clopidogrel treatment for hip-fracture patients is unknown. By continuously using multiple electrode aggregometry (MEA) at the authors' department they can fast-track non-responders to surgery despite clopidogrel treatment.

Innovations and breakthroughs

In this retrospective case-control study on patients with a proximal femoral fracture and concurrent clopidogrel treatment almost one third of patients with clopidogrel were non-responders, indicating that they had no effect of this treatment, or that they were not compliant to medication.

Applications

Analysis of variability in platelet aggregation using MEA can be used to identify non-responders and responders to clopidogrel treatment in hip fracture patients and they recommend this for emergency hospitals treating patients with acute proximal femoral fractures.

Terminology

Responders: (*i.e.*, to clopidogrel treatment): patients with anti-platelet effect of clopidogrel; Non-responders: Patients with no effect of treatment; MEA: A method to measure the effect of anti-platelet therapy *in vivo*.

Peer-review

The peer-reviewers pointed out that the study is also limited by intervention bias; MEA test was used to make clinical decisions such as platelet transfusions and surgical timing. These interventions could clearly have an effect on the results such as intraoperative bleeding as well as outcomes and differences between groups. The reviewers also pointed out the small sample and the retrospective design as limitations.

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