Bone Cement Implantation Syndrome

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INTRODUCTION

Bone cement implantation syndrome contributes substantially to morbidity and mortality in patients having cemented hip arthroplasty. The annual report of the national joint registry for England and Wales, recorded between 70,000 – 75,000 hip replacements are performed annually in England and Wales. Due to the ageing population it is a figure that is on the incline. (1)

Commonest reason for having total hip replacement in England and Wales, not so dissimilar to our local conditions, is due to disabling arthritis. THR and hemiarthroplasty are the management option for femoral fractures, as either primary or in the case of failed internal fixation. (2)

Additionally, patients over the age of 65 years often with co-morbidities, are most likely to require an anaesthetic for THR. Further contributing to the increase incidence of patients with an American Society of Anaesthesiologist Physical status classification of 2 or higher. (2)

National Institute of Health and Clinical Excellence (NICE) Guidelines on primary total hip arthroplasty, recommend the use of cemented prosthesis as they have better long-term viability. (1)

This has led to many questions being asked about the possible negative impact the use of bone cement has in orthopaedic practice, as many case reports, as well as published work has alluded to a link between bone cement and acute physiological deterioration. (2,3)

This booklet aims to cover some of the salient points of correctly recognizing and managing the complications related to bone cement implantation syndrome. Also to look at early markers for the patient population at risk, and latest evidence on surgical, and anaesthetic techniques to try and limit the risk that bone cement implantation syndrome (BCIS) poses to our patients undergoing THR. (1-3)
What is bone cement?

Sir John Chanley, has been recognized as the first surgeon to use bone cement in orthopaedics. (3) He, Sir John Chanley, used cold cured PMMA to attach an acrylic cup to the femoral head and to seat the metallic femoral prosthesis. (15)

As early as 1958, bone cement solely for the purpose for orthopaedic surgery was developed to perform specific functions such as:

- Affix the prosthesis
- Fastening of implant to bone
- Delivery device for antibiotics locally (3,5)

Polymethylmethacrylate (PMMA) is a type of bone cement commonly used for clinical applications in orthopaedic surgery. The word cement is misleading, as it implies that it binds two things together, when in fact it acts like space filler, which creates a tight space that holds the implant against the bone. (15) The reason for PMMA being so apt for these above mentioned functions, are owing to its unique physical and chemical properties. Although, bone cement itself has no adhesive properties, it depends on the close mechanical interlock between irregular bone surface and the prosthesis. (15)

The microscopic structure of bone cement includes two substances that are held together. The two components of bone cement are:

1. The supposed “pearls “ of bone cement consist of pre-polymerized PMMA particles, which are present in a white powder.
2. The liquid monomer of methyl methacrylate (MMA)

Table 1: Elements found in the composition of bone cement (3)

<table>
<thead>
<tr>
<th>PMMA 90%</th>
<th>Powder polymer: pre-polymerized PMMA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initiator: dibenzoylperoxide</td>
</tr>
<tr>
<td></td>
<td>Liquid monomer (MMA)</td>
</tr>
<tr>
<td></td>
<td>Activator: N,N-dimethyl-p-toluidine,</td>
</tr>
<tr>
<td></td>
<td>stabilizer: hydroquinone</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Gentamycin, Tobramycin, Clindamycin</td>
</tr>
<tr>
<td>Radiographic contrast material 10%</td>
<td>Ziconium dioxide or barium sulphate</td>
</tr>
</tbody>
</table>

The unique advantage of PMMA is that it cures rapidly and offers mechanical stability. (5,6)
Polymerization reaction \((3,5,6)\)

Upon mixing the two components of bone cement, namely the powder pre-polymer, also containing the initiator dibenzoylperoxide, and the liquid monomer (MMA), polymerization reaction will occur together with self-curing. The mixing of the substances can be done by hand or with the centrifugation or vacuum technologies. An important feature of bone cement is that it is heat sensitive, any change in temperature (albeit ambient, mixing components and mixing equipment) from the ideal temperature of 23 degree celsius affects the handling and setting time of the cement. As well as variations in humidity can affect setting time. Vacuum mixing of cement may speed up the setting time of cement. \((15)\) The average time that the polymerization reaction will last for is 2 – 5 minutes. Polymerization is an exothermic reaction, and can result in rather high temperatures in the femoral canal, or surface that the bone cement is being used for. Once the polymerization reaction is over temperature decreases and the bone cement becomes hard. \((3,5,6)\)

Phases of polymerization: \((3,5,6)\)

Initially the powder adsorbs the monomer liquid resulting in the formation of a viscous paste. The viscosity of the paste is dependent on the length of time the paste is left to cure.

Secondly, the hardening of the bone cement is as a result of a chemical process. The handling of bone cement can be divided into four phases, based on the varying degrees of viscosity.

1. Mixing phase to perfectly even out the powder and liquid.
2. Liquid phase is the non sticky state of bone cement
3. Working phase is the time that cement is injected
4. Hardening phase, which is a brief period between the final setting process and the development of polymerization heat. The temperatures may go as high as 70 – 120 \(^{0}\)C.

More importantly, the handling of bone cement is very dependant on the viscosity of the cement and the viscosity of cement is dependant on the length of time the paste is left to cure. High viscosity cement have better results in prosthetic fixation as compared to low viscosity cements. \((15)\)

Antibiotics and bone cement: \((3,5)\)

Antibiotic laden bone cement has long been accepted as an adjunct for treating localized established infection, i.e. osteitis. The role in infective prophylaxis is less clear. As studies have showed that resistance increases if bacteria exposed to antibiotic below the inhibitory dose for prolonged periods. Furthermore, there is still much debate about the choice of antibiotic, the duration of antibiotic activity, the method of preparation of antibiotic and the influence it has on the mechanical properties of bone cement.

The idea around antibiotic laden cement has been based on work done Bulchoz and Engelbrecht, that reported that penicillin, erythromycin, gentamycin introduced into the hip via bone cement, are able to penetrate the surrounding tissues for months, hence giving a prolonged local concentration of antibiotic.

Antibiotics may be used in high or low doses when mixed with bone cement, depending whether or not it is for treatment or prophylaxis. High dose antibiotic will be in the range of more than 2 g per 40 g of cement. Quite often it is 6 – 8 g of antibiotic mixed with 40 g cement. Low dose
antibiotic will be less than 2 g per 40 g of cement. As the preparation techniques of antibiotic laden cement have improved, the stability of the cement has improved also.

The factors influencing the release of the antibiotic are, the viscosity of the cement, by the surface of contact/exchange, by the conditions of the compound, and the type and amount of antibiotic.

Antibiotic laden bone cement has the advantage of having the antimicrobial work at the source of the infection, but it works best in combination with good sterile technique, and in combination with systemic antibiotics, with microbial directed therapy.

Below are two tables, the one outlining the ideal properties of an antibiotic in bone cement, the second one looking at the complications related to antibiotic laden bone cement.

**Table 2: Properties of the ideal antibiotic in bone cement** \(^{(7)}\)

<table>
<thead>
<tr>
<th>Requirement</th>
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<tbody>
<tr>
<td>Preparation must be thermally stable</td>
</tr>
<tr>
<td>Antibiotic properties not affected by heat</td>
</tr>
<tr>
<td>Must be water soluble for diffusion into tissues</td>
</tr>
<tr>
<td>Bactericidal</td>
</tr>
<tr>
<td>Must be released gradually over an appropriate time period</td>
</tr>
<tr>
<td>Minimal local inflammatory response</td>
</tr>
<tr>
<td>No resistance</td>
</tr>
<tr>
<td>Must have actions against common pathogens</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
</tr>
<tr>
<td>Coliforms</td>
</tr>
<tr>
<td>Anaerobes</td>
</tr>
<tr>
<td>Must not significantly compromise mechanical integrity</td>
</tr>
</tbody>
</table>

**Table 3: Complications of antibiotics in bone cement:** \(^{(3)}\)

<table>
<thead>
<tr>
<th>Complication</th>
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<tbody>
<tr>
<td>Attenuation of the structural and mechanical properties of bone cement</td>
</tr>
<tr>
<td>Antibiotic resistance</td>
</tr>
<tr>
<td>Allergic reaction</td>
</tr>
<tr>
<td>Systemic complications</td>
</tr>
<tr>
<td>Cost implication</td>
</tr>
</tbody>
</table>
Methods Of application of cement (15)

Digital

Mixing of cement is done by hand, until uniform paste/dough is formed. Ideally the surgeon will wait for the cement not to stick to glove before inserting the cement. It is an important step to wait for the cement to set as to early application of cement may lead to physiological changes i.e. drop in blood pressure.

Once the cement is in then the prosthesis should be held in place until cement hardens.

Syringe Application of cement

I.e. cement gun, is used it is advisable to use bone restrictor, at the required depth into the prepared bone cavity. As the cement will be applied in retrograde fashion and then to maintain adequate pressure until cement has hardened.

Vacuum mixing and delivering

The advantage of this technique is that it reduces monomer evaporation and exposure in theatre. Furthermore, it yields a homogenous mix without affecting the viscosity of the cement.

Pressurization

Allows the bone cement time to set in the canal, and not be pushed out of the bone. The pressure generally has to be kept above systolic pressure. The advantages of pressurization are, greater penetration of the bon, improves bone –cement interface an increases the fatigue strength of the cement.

Cement restrictors

They are merely intramedullary plugs used in hip arthroplasty to achieve good filling and pressurization, which will have the advantage of causing greater penetration of the cement, hence enhancing prosthetic stability.

Preparing the bone bed for cementation

In order to have the best outcome for fixation of prosthesis using bone cement a few prerequisites that need to be in place

1. A clean bone bed, brush and lavage
2. Injecting cement until its of a high viscosity – thereby preventing blood to penetrate the cement
3. Pressurizing the cement by using a cement gun.

Cementing Techniques – The Evolution (15)

The continuous advancement in cementing can be classified from first to third generation techniques, with the changes occurring in bone bed preparation, cement preparation and cement delivery.

First generation cementing technique

- Hand mixing of cement in bowels
- Minimal preparation of the femoral canal and cancellous bone left in situ
- The canal was irrigated and suctioned prior to digitally placing cement

Second generation cementing techniques:
- All cancellous bone removed and distal cement restrictor used
- Pulsatile irrigation, packing and drying of the canal
- Cement gun used in retrograde fashion

Third generation cementing techniques:
- Vacuum-centrifugation used to prepare cement
- Femoral canal irrigated with pulsatile lavage and packed with adrenaline soaked gauze
- Now prosthesis inserted using stabilizers.

Bone Cement Implantation Syndrome

Bone cement implantation syndrome (BCIS) is characterized by sudden physiological fall out, of which hypoxia, hypotension, cardiac arrhythmias, increase in pulmonary vascular resistance and at its most catastrophic can lead to cardiac arrest and death. (2,8) All procedures requiring bone cement may result in BCIS, however it has been particularly highlighted in the elderly frail patients having cemented arthroplasty following hip fractures. BCIS commonly occurs during one of the five stages in the surgical procedure: femoral reaming, acetabular or femoral cement implantation, insertion of the prosthesis or joint reduction. (2)

A key factor for the medical team dealing with patients undergoing THR, is to understand how to minimize the complications, through modern cementing techniques, appropriate anaesthesia intervention and adequate patient preparation, and possibly to reconsider the widespread use of bone cement. (9)

Severity classification of bone cement syndrome

*Table 4: Incidence of adverse effects during arthroplasty using cemented prosthesis* (10)

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Moderate hypoxia SpO2 &lt; 94% and systolic BP &gt; 20 % decrease</th>
<th>+/- 20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>Severe hypoxia (SpO2 &lt; 88% and systolic BP decrease &gt; 40% with an unexpected loss of consciousness)</td>
<td>+/- 3%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Cardiopulmonary collapse requiring cardiopulmonary resuscitation</td>
<td>+/- 1%</td>
</tr>
</tbody>
</table>
Table 5: A complete list of characteristics to look for in keeping with BCIS

<table>
<thead>
<tr>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Systemic, life-threatening hypotension</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Increased central venous pressure</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
</tr>
<tr>
<td>Bronchoconstriction</td>
</tr>
<tr>
<td>Anoxia/hypoxaemia</td>
</tr>
<tr>
<td>EtCO₂ decrease</td>
</tr>
<tr>
<td>Cardiac dysrhythmia</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
</tr>
<tr>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>Sudden death</td>
</tr>
<tr>
<td>Fat/marrow emboli</td>
</tr>
<tr>
<td>Hypothermia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
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</table>

Incidence of bone cement implantation syndrome

Paul D Rutter, Sukhmeet Panesar et al, in their article; “What is the risk of death or severe harm due to bone cement implantation syndrome among patients undergoing hip hemiarthroplasty for fractured neck of femur? A patient safety surveillance study”, capturing data from the National Reporting and Learning System NRLS, from 1 January 2005 to 31 December 2012, concluded that the risk is one death or severe harm per 2900 cases, although this conclusion is limited by under reporting. Most of the reports, of this study found that BCIS, occurred few minutes after cementation, and all of the deaths occurred on the table.

Highlighting again the importance of being vigilant whilst patient on the table and in theatre.

Aetiology of bone cement implantation syndrome

The aetiology of bone cement syndrome remains uncertain, and consequently has resulted in many hypothesis, as follows:

1. Air or gas embolisms as a result of polymerization of methyl methacrylate monomer (MMA).
2. The direct effect of the exothermic reaction on cement pressure.
3. Hypersensitivity reaction to the bone cement, more specifically the acrylic monomer
4. Reflex bradycardia
5. The exponential rise in intramedullary pressure following the insertion of hot acrylic cement. Hence, force fat and marrow into the circulation resulting in pulmonary emboli
6. Fat and debris from the femoral shaft embolize from the canal during cement implantation and implant insertion
7. The direct depressant effects of the monomer (may augment the cardiovascular depressant effects of volatile anaesthetic agents
8. The direct vasodilatory effects of the monomer if absorbed into the circulation
9. High amount of the monomer absorbed from the vascular femoral shaft
10. Small amounts of toxic, unreacted methyl methacrylate monomer absorbed rapidly into the circulation
11. Embolic showers that occur during cement pressurization

Monomer –mediated model (2)

Circulating MMA has been shown in vitro studies to cause vasodilatation. However the concentrations needed to achieve this in vivo following hip arthroplasty is considerably lower than the concentrations required to cause vasodilatation and pulmonary vascular constriction.

Consequently, the haemodynamic changes are suggested to be as a result of intramedullary pressure increase, leading to cement emboli causing many of the changes we see in patients with BCIS.

Embolic model (2)

Emboli have been easily detectable using echocardiography in the right atrium, right ventricle and pulmonary artery during surgery. Furthermore, emboli have been seen in post mortem autopsies. The physiological changes observed in BCIS may be as a result of both mechanical and mediator release, which stimulates pulmonary vasoconstriction.

Mechanism of emboli formation (2)

Embolization is as a result of the sharp rise in intramedullary pressures developing during cementation and prosthesis insertion.
As the cement undergoes its exothermic reaction and expands in the space it forces the air, fat globules, debris and mma into the circulation.

The temperature increase can be quite significant within 6 min after mixing the components. Cementation can be achieved either by manually placing it or by cement gun into the femoral canal. The pressure of cement when using the gun as opposed to doing it manually, nearly doubles. Studies have shown decrease in pressure when a venting hole, is drilled proximally into the femoral canal.

Transoesophageal Echocardiography (2)

Ereth, Weber and Abel et al., demonstrated in their paper that more emboli were detected on echocardiography in cemented arthroplasty than in uncemented patients. Interestingly the amount of emboli detected, had no correlation with the physiological changes detected clinically.

Figure 1: four chamber TOE views showing embolism during total hip arthroplasty. First picture moving, top left, Small emboli (<5mm) filling less than half the right atrium. Top right: Medium sized emboli (5-10mm, arrowed) and small emboli filling more than half the right atrium. Bottom left: small emboli <5mm, completely filling the right atrium, multiple paradoxical emboli seen in left atrium. Bottom right: Large emboli (>10mm) in the right atrium with delayed passage at the tricuspid valve. (2)
**Mediator Model** \(^{(2,8)}\)

Mediator model suggests that pulmonary vasoconstriction can be as a result of mediators being released from the endothelial lining after being mechanically stimulated, or as a result of pro-inflammatory mediators that results in an increase in pulmonary vascular resistance.

**Histamine release and Hypersensitivity** \(^{(2,8)}\)

Due to the relative acute onset of symptoms following the insertion of bone cement, and the laboratory finding of raised histamine, may point to an element of hypersensitivity to the monomers. However, there is no evidence to date that suggests that BCIS is an hypersensitivity reaction. The importance of the raised histamine post cementation remains uncertain.

**Complement activation** \(^{(2,8)}\)

C3a and C5a are potent mediators of vasoconstriction, hence it is believed to play a role in the increase in PVR, following bone cement insertion as the blood count of these factors are much higher than in patients having uncemented hemiarthroplasty.

In reality, it most likely that all these models, theories play a part and results in the clinical syndrome of BCIS.

**Patient risk factors for BCIS** \(^{(1,8,10)}\)

Pre existing disease
Pre – existing pulmonary hypertension
Significant cardiovascular disease
NYHA class 3 or 4
Canadian Heart Association class 3 or 4
Surgical factors
Pathological fracture
Inter-trochanteric fracture
Long-stem arthroplasty

**Surgical Risk Factors** \(^{(1,8,10)}\)

The long stem femoral component places the patient at higher risk for developing bone cement implantation syndrome, as opposed to the shorter stem prosthesis. Furthermore, previously un-instrumented femoral canal may place a patient at a higher risk than previously instrumented canal.

**Anaesthetic Risk Reduction** \(^{(14)}\)

An observational study of 65 535 patients’ data collection over one year period, did not find any significant difference in 30 day mortality between patients administered a general anaesthetic or neuraxial technique for surgical repair of hip fractures.

The main focus for the anaesthetist would be to recognize the at risk patient for developing bone cement implantation syndrome. Monitoring for it, and making sure that the patient is kept haemodynamically stable.
Prevention of BCIS \(^{(1, 8, 10)}\)

According to the 2015 guidelines, (a consensus document produced by expert members of a working established by the association of anaesthetist of Great Britain and Ireland, British orthopaedic association and British geriatric society) that there should be a three-stage process to reduce the incidence of problems in patients undergoing cemented hemiarthroplasty for hip fractures:

1. Identification of patient that are at high risk of cardio-respiratory compromise:
   - Increasing age
   - Significant cardiopulmonary disease
   - Diuretics
   - Male sex

2. Preparation of teams and identification of roles in case of emergency.
3. Pre – operative multidisciplinary team discussion when appropriate
4. World Health Organization Safe Surgery Checklist

Specific intra – operative roles for all the parties involved \(^{(1, 8, 10)}\)

**Surgeon:**

Inform the anaesthetist that you are about to insert cement.

Thoroughly wash and dry the femoral canal achieving adequate heamostasis

Apply cement gun with a suction catheter and intramedullary plug in the femoral shaft

Avoid vigorous pressurization of cement in patients at high risk of cardiovascular compromise

**Anaesthetist**

Ensure adequate resuscitation

Spinal or general anaesthesia

Confirm that you are aware that they are about to insert cement

Monitor vital signs, and in higher risk patients more invasive monitoring are stable. Inform the surgeon of any change in physiological status

**Management of bone cement implantation syndrome** \(^{(10)}\)

BCIS may be reversible with prompt recognition and early physiological support, to maintain both coronary perfusion pressure and right heart function.
It is a careful balance of optimizing preload, and increasing contractility, hence improving the right ventricular perfusion pressure, to meet the increased oxygen demand caused by the syndrome.

The important aspect with managing BCIS is that it is a time limited process and most often the pulmonary pressures normalize within 24 hours. BCIS is reversible as long as the haemodynamic stability is maintained by supportive therapy.

The most important factor of surviving the embolic load is the heart’s ability to maintain adequate right ventricular output during increased pulmonary vascular resistance. The essential characteristic during and after embolization is the ability to increase the heart rate in the presence of decreased stroke volume.

CONCLUSION

Total hip replacement and hemiarthroplasty procedures are on the increase globally as well as in South Africa. Due to improving living conditions, and better health practices we are dealing with an increase in elderly patients with a myriad of co-morbidities, that we will have to manage in our daily practice as anaesthesiologists.

By actively engaging our patients with a multidisciplinary approach to their healthcare, we may improve and reduce some of these negative outcomes associated with Hip arthroplasty.
REFERENCES


9. Xiangbei Q, Yingze Zhang, Jinshe Pan,


