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REVIEW

Antibiotic-free antimicrobial poly (methyl methacrylate) bone cements: A state-of-the-art review

Gladius Lewis

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Abstract

Prosthetic joint infection (PJI) is the most serious complication following total joint arthroplasty, this being because it is associated with, among other things, high morbidity and low quality of life, is difficult to prevent, and is very challenging to treat/manage. The many shortcomings of antibiotic-loaded poly (methyl methacrylate) (PMMA) bone cement (ALBC) as an agent for preventing and treating/managing PJI are well-known. One is that microorganisms responsible for most PJI cases, such as methicillin-resistant *S. aureus*, have developed or are developing resistance to gentamicin sulfate, which is the antibiotic in the vast majority of approved ALBC brands. This has led to many research efforts to develop cements that do not contain gentamicin (or, for that matter, any antibiotic) but demonstrate excellent antimicrobial efficacy. There is a sizeable body of literature on these so-called "antibiotic-free antimicrobial" PMMA bone cements (AFAMBCs). The present work is a comprehensive and critical review of this body. In addition to summaries of key trends in results of characterization studies of AFAMBCs, the attractive features and shortcomings of the literature are highlighted. Shortcomings provide motivation for future work, with some ideas being formulation of a new generation of AFAMBCs by, example, adding a nanostructured material and/or an extract from a natural product to the powder and/or liquid of the basis cement, respectively.

Key Words: Periprosthetic joint infection; Poly (methyl methacrylate) bone cement; Antibiotic-loaded poly (methyl methacrylate) bone cement bone cement; Antibiotic-free antimicrobial poly (methyl methacrylate) bone cement bone cement

Core Tip: Although antibiotic-loaded poly (methyl methacrylate) (PMMA) bone cements are widely used both as prophylactic agent and in the treatment/management of prosthetic joint infection, there is dissatisfaction about the material. A new generation of antibiotic-free antimicrobial PMMA bone cements (AFAMBCs) is emerging. The present review is a critical appraisal of the literature on AFAMBCs, highlighting its strengths, shortcomings, and possible areas for future studies. The conclusion is that state-of-the-art on AFAMBC formulations is such that it is premature to comment on the potential of any of the formulations for clinical application.

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INTRODUCTION

Regardless of the patient group, periprosthetic joint infection (PJI) is a relatively rare occurrence; for example, 2 years after total hip arthroplasty (THA) and total knee arthroplasty (TKA), the cumulative incidence rate is on the order of between 0.5% and 0.8% and about 1.0% of cases, respectively[1,2]. Nonetheless, PJI is recognized as being the most challenging of complications of total joint arthroplasties (TJAs) (to the point of intractability) because of the associated risk for revision of the implant, increase in mortality, increase in morbidity, decrease in quality of life of the patient, and increased direct and indirect costs[3,4]. As such, PJI has been the subject of myriad studies, the bulk of which has been devoted to four aspects, these being identification and stratification of patient- and surgery-based risk factors, diagnosis, prevention, and treatment/management[4]. Among risk factors, the significant roles of morbid obesity (body mass index greater than 40 kg/m^2), young age (< 50 years) of the patient, preoperative use of opioids by the patient, and prolonged surgery time (> 2 h) are recognized even though the supporting clinical evidence ranges from limited to moderate[5-8]. With respect to diagnosis, an assortment of methods is in current clinical use, such as ^{18}F-labeled fluorodeoxyglucose-positron emission tomography (FDG-PET)[9], and measurement of synovial fluid biomarkers, notably, alpha-defensin[10], or under investigation, among which are measurement of temporal change in D-dimer level in conjunction with serum erythrocyte sedimentation rate and C-reactive protein level[11], use of monocyte/lymphocyte ratio, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio (PLR), and platelet/mean platelet volume ratio (PVR), in conjunction with other hematologic and aspirate markers [12], and landmark-guided hip aspiration[13]. To date, a gold standard has not emerged. The most widely used prevention method is anchoring the implant in a bed of antibiotic-loaded poly(methyl methacrylate) bone cement (ALBC)[4]. As for treatment/management, the two common approaches are: (1) Surgical debridement (debridement followed by intravenous or highly bioavailable oral delivery of antimicrobial medication specific to the microorganism found in the case (medical therapy) and retention of the implant (DAIR)[14,15]); and (2) Resection arthroplasty using two-stage exchange[16,17] (although, in recent years, in some countries, enthusiasm is being shown for one-stage exchange[18,19] followed by medical therapy[4,16]). In either option, it is common to fix the exchanged implant to the contiguous bone in an ALBC bed[16].

While an ALBC has a number of attractive features, chief among which are ease of preparation in the operating room and low intrinsic toxicity, it has its share of shortcomings and concerns. One shortcoming is its lack of bioactivity[20,21]. Another is the fact that the bacterial species that are responsible for PJI, most commonly, *S. aureus* and *S. epidermidis*[22], are becoming resistant to gentamicin sulfate, which is the antibiotic in the vast majority of ALBC brands approved by national regulatory bodies, such as the US Food and Drug Administration (the method of mixing of the antibiotic with the cement powder is proprietary) and physician-directed ALBC formulations (mixing of antibiotic and cement powder is carried out in the operating room)[4,23]. A third shortcoming is that the release profile of the antibiotic is sub-optimal, being characterized by 1) an initial short high release rate (zone lasts, typically, < 2 d), followed by a significant reduction in release rate, culminating in exhaustion of release after, typically, 20-30 d and 2) cumulative release of only, typically, between about 0.3% and about 13% of the loaded antibiotic[24,25]. Additionally, there is a lack of consensus that even with risk-stratified usage in primary TJA, the current generation of ALBCs is efficacious and cost-effective[26-36]. As for concerns about ALBC, there are long-standing ones, such as potential deleterious effect on mechanical properties of basis cement[37], and ones that have only recently been raised, such as an increase in immunological factors (specifically, soluble interleukin-6 and C-reactive protein) in patients in which there is a gentamicin-loaded cement implant, suggesting that unknown immunomodulatory pathways may be altered by an ALBC[38].

The aforementioned observations highlight the need for novel methods for reducing the risk for PJI whether ALBC is used as a prophylactic agent in primary THAs and TKAs (as is common practice in a number of countries, such as Norway, and limited use in others, such as United States) or during the second stage of a two-stage exchange arthroplasty (as is common practice in the United States[39]). This need has served as the driver for the large amount of research attention that has been given to this field. These efforts may be grouped into four approaches: application of an antimicrobial coating to part(s) of implant component(s), such as the proximal zone of the femoral stem of a THA[4,40-45]; use of ALBCs in which a relatively new antibiotic/antibacterial compound (for example, daptomycin[46] or a second-generation lipophosphonoxin[47]) is added to the cement powder; modification of the surface of the implant (for example, incorporation of an antibiotic-releasing polymer into the surface of a joint implant [48] and use of a nanofabrication method to create biomimetically-inspired nanostructures on an implant surface[49]); and proposed use of antibiotic-free antimicrobial PMMA bone cements (AFAMBCs)[50-68]. The focus of the present review is AFAMBCs, which have been the subject of many studies on their formulation and characterization[50-68]. However, to date, only one review of this body of literature has been published[69] but it has two shortcomings. First, only about half of that review was devoted to AFAMBCs, with the balance being on aspects such as PMMA bone cement and orthopaedic infections in general and details of the classification, diagnosis, and treatment of PJI. Second, some of the literature studies reviewed were not appropriate to bone cement use in TJAs; for example, the subject of the studies was cement for beads, blocks, and spacers for the treatment of severely contaminated open tibial fractures[70], bone reconstruction[71,72], cement used for stabilizing/augmenting fractured osteoporotic vertebral body fractures (for example, *via* vertebroplasty or balloon kyphoplasty)[73], and antibacterial coatings[74].

The present work focuses exclusively on the literature on AFAMBCs for long-term load-bearing TJA applications (as such, it excludes its use in spacers and blocks), giving a comprehensive and critical review of this body of knowledge by not only summarizing key results (with special emphasis on evaluations of antimicrobial efficacy and cytotoxicity) but, also, highlighting attractive features and shortcomings of literature studies. The latter feature should point to opportunities for future research in the field. This review should inform discussion of the potential for use of AFAMBCs to replace ALBCs.

LITERATURE STUDIES

Antimicrobial activity

The activity of a bone cement, in which the powder additive comprised NanoSilver particles (silver particles, of size 5-50 nm and porosity 85%-90%) (loading between 0% and 1%), when tested against a clinical isolate of MRSE showed loading dependency, with increased loading of the additive leading to increased activity; specifically, cement having a loading of 1% of the additive producing complete inhibition of proliferation of the bacterial strain. As a reference, uninhibited proliferation of the strain occurred when an approved ALBC brand (that contained 2% gentamicin) was used[50]. This same comparative trend was found when 1% NanoSilver-loaded cement was compared with the approved ALBC brand when a clinical isolate of *S. epidermidis* was used[50].

Chitosan (CS) nanoparticles (CS-NPs) (diameter: 220 ± 3 nm) were prepared using the ionic gelation method and quaternary ammonium chitosan (QCS) was synthesized by the method presented by Huh *et al*[75] QCS NPs (mean diameter: 284 ± 2 nm) were obtained from QCS in the same manner as was done for CS-NPs. Two approved plain ALBC brands and two approved ALBC brands were used as negative and positive control cements, respectively. Two sets of experimental AFAMBCs were formulated, one by adding CS-NPs to the cement powder and the other by adding QCS-NPs to the cement powder[51]. Against both *S. aureus* and *S. epidermidis*, each of the AFAMBCs showed significant improvement in antimicrobial activity compared to a control cement, but with QCS-NP-loaded cement showing significantly higher activity than the CS-NP-loaded cement[51]. These results were attributed to the fact that the NPs provide a high surface charge density for interacting with and disrupting bacterial cell membranes[51].

An experimental AFAMBC was obtained by mixing a monomer of quaternized ethylene glycol dimethacrylate piperazine octyl ammonium iodide (QAMA) into the liquid of an approved plain ALBC brand (10, 15, and 20 wt/wt%) (designated PMMA-10QAMA, PMMA-15QAMA, and PMMA-20QAMA cements, respectively)[52]. While *Escherichia coli* (*E. coli*) was retained on the surface of plain cement specimens, there was no evidence of retention and aggregation on experimental AFAMBC specimens. The antimicrobial action displayed by the AFAMBCs was attributed to the presence of QAMA, a polymerizable monomer that has an irreversibly bound component[52].

Using a novel synthesis route, Ag nanoparticles (AgNPs) with very well controlled geometrical properties and stability were obtained and, then, these particles were capped with tiopronin (TIOP), an agent that allows binding of other compounds to the nanoparticles[54]. These nanoparticles (AgNPs-TIOP) were added to the powder of a plain PMMA bone cement (0.1%, 0.5%, and 1.0%)[54]. Against gram-positive methicillin-resistant *S. aureus* (MRSA), the difference in growth rate of the bacterial strain when specimens of the experimental AFAMBC (1% of mean diameter 11 nm Ag-TIOP nanoparticles)

and those of a control cement (no Ag nanoparticles) were used was not significant but the lag time (directly related to resistance to growth of the bacterial strain) of the AFAMBC was approximately 12 times longer than that the control cement specimens were used, indicating the better antimicrobial performance of the former cement[54]. Although the exact mechanism responsible for the antimicrobial activity of Ag nanoparticles has not been established, many explanations have been put forward. Examples are uptake of free Ag ions followed by disruption of the production of an energy storage molecule (adenosine triphosphate (ATP)) and replication of DNA[76]; inactivation of the bacterial cell (cell membrane and enzymes) by the Ag ions interfering with enzymes that interact with sulfur in the protein chains and/or generating reactive oxygen species[54], which kill the cells; and Ag ions causing separation of paired strands of DNA in the bacteria[77].

A bioactive glass (SiO_2-Na_2O-CaO-P_2O_5-B_2O_3-Al_2O_3-Ag_2O) was produced by melting the reactants in a Pt crucible at 1450 °C, then quenching the melt in water to obtain a frit that was milled and sieved to yield glass powder (SBAG powder) (grain size < 20 mm)[55]. An experimental AFAMBC was obtained by mechanically mixing SBAG powder with the powder of an approved plain cement brand (loading: 30% and 50%), with two brands being used as control, one classified as low-viscosity (LV) and the other high-viscosity. Against *S. aureus*, a small drop in both proliferation and adhesion were observed when an AFAMBC rather than a control cement was used, with the same trends being seen in the values of the McFarland Index[55]. In an inhibition halo test, as expected, the size of the halo zone when AFAMBC specimens were used decreased with length of time of contact of the specimens with the agar substrate but, importantly, at the end of the 2nd day, the inhibition zone measured between approximately 1.0 and approximately 1.5 mm, indicating that the antibacterial capability of the cements is good[78,79]. The antimicrobial activity of a bioactive glass has been attributed to an increase of aqueous pH and osmolarity in the *in vivo* zone that surrounds the glass, which accompanies the dissolution of the glass [80], and deposition of glass debris on the surface of the bacteria[81].

Organic nanoparticles containing propylparaben were prepared by fast simultaneous removal of solvents and water from a volatile oil-in-water microemulsion composed of polypylparaben, *n*-butyl acetate, iso-propyl alcohol, sodium dodecyl sulfate (SDS), polyvinylpyrrolidone (PVP), and water, resulting in a fine powder composed of propylparaben nanoparticles (16 wt/wt%), SDS (45 wt/wt%), and PVP (39 wt/wt%)[56]. An AFAMBC was formulated by adding this fine powder to the powder of an experimental plain bone cement formulation (0.1%, 0.5%, 1%, 2%, 5%, and 7%). Overall, against a given bacterial strain (*S. aureus*, MRSA, or *S. epidermidis*), the duration of the lag phase increased but the growth rate (GR) decreased with increase in concentration of nanoparticles in the AFAMBC[56]. These trends suggest that the antimicrobial effect of the AFAMBC is a consequence of the conjoint reduction of viable microbial population and the viable cells not exhibiting the same phenotype of the cells in contact with the nanoparticles[56].

A modified Tollens method that involved reduction of $AgNO_3$ to metal Ag by use of a glucose was used to synthesize Ag nanoparticles (AgNPs), which were then capped with oleic acid (OA) (Ag NPs-OA)[57]. These Ag NPs-OA were loaded into the powder of a plain PMMA bone cement (0.01, 0.05, and 0.10%)[57]. Against *S. aureus*, the mean duration of the lag phase (l) and the growth rate (GR) was between 5 and 6 times longer and between 2 and 3 lower on specimens of AFAMBC (0.05% AgNPs) compared to the corresponding values for plain cement (control cement) specimens, with the trend being the same when MRSA was used[57]. However, when *S. epidermidis* was used, the ratio for either l or GR was much smaller (approximately 1.4)[57].

An AFAMBC was formulated by mixing commercially-available Ag nanoparticles (diameter: 30-50 nm), which had been surface-functionalized with polyvinylpyrrolidone (0.2 wt/wt%) to aid dispersion and minimize agglomeration of the particles, into the liquid of an approved plain cement brand or an approved ALBC brand (loading ratio: 0.25%, 0.50%, and 1.0%, relative to mass of its powder) using an ultrasonic homogenizer with a solid Ti tip[58]. Using a modified Kirby-Bauer disk diffusion assay, it was found that against each of the bacterial strains used (commercially-available *S. aureus* and *S. epidermidis* and 4 clinical isolates obtained from patients with active PJIs (2 *S. aureus* and 2 *S. epidermidi* s)), none of the AFAMBCs demonstrated antimicrobial activity (that is, there was a large area of bacterial colony growth) while the positive control (an approved ALBC brand; antibiotic: gentamicin) exhibited large zones of inhibition (about 18-39 mm)[58]. Similar trends were found in the results of studies in which time-kill assays against planktonic bacteria were performed[58]. However, results of bacterial adhesion tests showed that each of the AFAMBCs significantly reduced biofilm formation relative to the plain cement[58]. These results suggest that while the AFAMBCs have no antimicrobial activity against planktonic bacteria, they have good potential for use in cases where prevention of bacterial adhesion is needed (for example, in primary TJAs)[58]. It is to be noted that: (1) Many of the bacteria commonly involved in PJI, such as *S. aureus*, produce a biofilm, which is a community of microorganisms embedded in an organic polymer that mainly is composed of polysaccharides, proteins, extracellular DNA and lipids, that adheres to an implant surface[82]; (2) A biofilm allows planktonic cells to change their mode of growth to the sessile form[82]; and (3) It is expected that a biofilm will protect the dividing bacteria from the action of an AFAMBC[82,83].

An experimental AFAMBC was formulated by adding a first-generation quaternary ammonium dendrimer of tripropylene glycol diacrylate (TPGDA G-1) to the liquid of a commercially-available plain bone cement (5, 10, 15, or 20 wt/wt%)[59]. Against a commercially-available *S. aureus* strain, the mean

antimicrobial efficiencies of 5TPGDA cement and 10TPGDA cement were 45% and 100%, respectively, compared to a negligible amount for the plain cement counterpart[59]. The antimicrobial action of the quaternary ammonium dendrimer was attributed to it breaking the wall and membrane of the microorganism[59].

A bioactive glass (SiO_2-Na_2O-CaO-P_2O_5-B_2O_3-Al_2O_3) was produced by melting the reactants in a Pt crucible at 1450 °C for 1 h, then quenching the melt in water to obtain a frit that was milled and sieved to yield glass powder (SBA2 powder) (grain size < 20 mm)[60]. This powder was then subjected to an optimized ion-exchange process in aqueous solution of $AgNO_3$, after which the silver-doped powder was dried in air at 60 °C (Ag-SBA2 powder). The experimental AFAMBC was obtained by mechanically mixing 30 wt% of Ag-SBA2 powder with the powder of an approved plain cement brand (Ag-SBA2 cement), with three approved plain PMMA cement brands being used as controls. Against a commercially-available stock of *S. aureus*, 1) a significant drop in both proliferation and adhesion were observed when the AFAMBC rather than a control cement was used, trends that were also seen in the values of the McFarland Index; and 2) in an inhibition halo test (Kirby-Bauer test), the size of the halo zone when AFAMBC specimens were used was between approximately 2.5 and approximately 3.0 mm[60].

An AFAMBC was formulated by mixing commercially-available gold nanoparticles (Au NPs; 99.95% purity; diameter: 10-20 nm) with the powder of an approved plain bone cement brand (loading: 0.25, 0.50, and 1.00 wt/wt%)[61]. Against clinical isolates of MRSA, 1) live bacterial cells were reduced by up to approximately 55% on specimens of cement containing 1 wt/wt% Au NPs compared to specimens of the control cement (no loaded Au NPs); and 2) three-dimensional reconstruction of the biofilm showed a drop of biofilm thickness by approximately 74% when an ALAMBC was used[61].

A bioactive glass (SiO_2-Na_2O-CaO-P_2O_5-B_2O_3-Al_2O_3) was produced by melting the reactants in a. Pt crucible at 1450 °C for 1 h, then quenching the melt in water to obtain a frit that was milled and sieved to yield glass powder (SBA3 powder) (diameter < 20 mm)[62]. This powder was then subjected to an optimized ion-exchange process in a copper-containing aqueous solution, after which the Cu-doped powder was washed, filtered, and dried in air at 60 °C (Cu-SBA3 powder). An experimental AFAMBC was obtained by mechanically mixing 10 wt% of Cu-SBA3 powder with the powder of an approved plain cement brand, with three approved plain PMMA cement brands being used as controls[62]. Against *S. epidermidis* biofilm, a significant drop in bacteria viability was observed at each assayed time-point when an AFAMBC rather than a control cement was used (by a factor of between 2 and 4), indicating that the antibacterial potential of the AFAMBC is good[62]. The antibacterial action of the Cu-SBA3 cements was explained in terms of participation of reactive hydroxyl radicals that are generated in reactions that are harmful to cellular molecules, such as oxidation of proteins[77]. Notwithstanding these results, the resistance of some bacterial species, such as *E. coli*, against copper-containing biomaterials, was noted[62].

A bioactive glass (SiO_2-Na_2O-CaO-P_2O_5-B_2O_3-Al_2O_3) was produced by melting the reactants in a Pt crucible at 1450 °C, then the melt was quenched in water to obtain a frit that was milled and sieved to yield glass powder (SBA2 powder) (grain size < 20 mm or 20-45 mm)[63]. This powder was subjected to an optimized ion-exchange process in aqueous solution of $AgNO_3$, after which the silver-doped powder was dried in air and stored (Ag-SBA2 powder). An experimental AFAMBC was obtained by mechanically mixing 15 or 20 wt% of an Ag-SBA2 powder with the powder of an approved plain cement brand. Several combinations of process variables for producing the powder (drying temperature, storage mode, and mixing temperature) were used, resulting in 8 variants of powders. In an inhibition halo test in which a commercially-available *S. aureus* strain was used, the size of the halo zone when AFAMBC specimens were used was between approximately 2 and approximately 4 mm, indicating marked antibacterial activity of these cements[63].

An AFAMBC was prepared by incorporating sheets of CS and/or graphene oxide (GO) nanosheets, synthesized using the protocols given by Mangadlao *et al*[84], into the liquid of an experimental plain PMMA bone cement (CS- and GO-based cements)[64-66]. A plain cement served as the control cement. Against a commercially-available *S. aureus* strain, after 24 h incubation, the cements containing 0.2% GO (ABC-0.2GO cement), 0.3% GO (ABC-0.3GO cement), 0.5% GO (ABC-0.5GO cement), or 15% CS (ABC-15CS cement) showed significantly higher antimicrobial activity compared to that of the control cement [64,65]. Two mechanisms were postulated to explain the antimicrobial activity of the GO-based cement [64]. First, GO sheets directly contact the bacterial cell, thereby damaging them. Second, reactive oxygen species that are produced destroy the cell membrane subsequent to the GO sheets contacting the surface [64,65]. Synergistic antimicrobial activity was demonstrated in the cement that contained 0.5% GO and 15% CS (ABC-0.5GO-15CS cement)[64].

An experimental AFAMBC formulation (PMMA-NAC cement) was obtained by adding N-acetylcysteine powder (NAC) (an antibacterial agent) to PMMA bone cement in loadings ranging from 10 to 50% wt/vol[67]. At NAC loading ≥ 20% wt/vol, the antibacterial efficacy of the NAC-PMMA cement against planktonic forms of *S. aureus* and *E. coli* was significantly greater than that of the control cement (an approved plain cement brand). The same trend was seen against biofilm forms of the same bacterial strains.

Two variants of an experimental AFAMBC were prepared, the first one by mixing particles of a 5 wt/wt% of a bioglass (BGII-0.4; grain size: ≥ 40 mm), Ag NP powder (particle size: approximately 50 nm) (1.5 wt/wt%), and the powder of an approved plain cement brand (BC-BGII-0.4-AgNP cement)

[68]. BGII-0.4 was prepared using the Stober method modified by Zheng *et al*[85]. The composition of the other variant was the same that of the first one with the exception that a different bioglass was used (a sol-gel obtained SiO_2/CaO (70/30 mol%) bioglass; grain size: about 300 nm) (BG-MP)[68]). The antibacterial performance of each of the AFAMBC variants was determined in two tests using a hospital strain of *S. aureus*: inhibition of the growth of the strain after 4 h and effectiveness (methicillin resistance). In each of these tests, the BC-BGII-0.4-AgNP cement showed significant improvement compared to the control cement (an approved plain cement brand)[68].

In vitro cytotoxicity/cytocompatibility

On L929 mouse fibroblasts, the difference in release of lactate dehydrogenase (an indicator of cell integrity) when an experimental AFAMBC (NanoSilver-loaded cement) was used *vs* when an approved ALBC (control cement) was used, in a non-toxic cell culture medium, was not significant, a trend that was also observed both with protein content and number of vital cells, all of which showed that the lack of cytotoxicity of the AFAMBC[50]. Furthermore, on a human osteoblast cell line (hFOB), only a few dead osteoblasts were seen in live-dead staining in the NanoSilver bone cement specimens and osteoblasts that grew on these specimens were, in the main, vital and grew in a mesh-like manner, as just as in the cell culture medium, showing that the cement has high biocompatibility[50]. The results were explained in terms of Ag ions binding to cellular structures in the bacterial strain (especially, to their SH- groups), thereby interfering with the integrity, energy production, and conservation of the bacterial cell[50]. In contrast, bacterial resistance to the antibiotic in the control cement (gentamicin), being an aminoglycoside, can be acquired by single point mutations [50].

On mouse fibroblast cells (3T3), the difference in cytotoxicity between an experimental AFAMBC (15% CS-NPs or 15% QCS-NPs added to cement powder) and a negative control cement was not significant[51]. There was good adherence of cells (a commercially-available human osteosarcoma cell line; HOS TE85) on specimens of PMMA-15QAMA cement after 1 wk, indicating cytocompatibility of the cement[52].

On osteoblast cells (MC 3TC), the difference in cytotoxicity between the Ag nanoparticles-tiopronin cement and the control cement (an approved plain ALBC brand) was not significant, regardless of the nanoparticles loading of the cement[54].

On osteoblast cells (MC-3T3), the difference in cytotoxicity between an experimental AFAMBC (contained Ag NPs-TIO) and a counterpart control cement (same composition but no Ag NPs-TIO) was not significant regardless of the duration of exposure to the cells[56]. On osteoblast cells (MC-3T3), the difference in cytotoxicity between an experimental AFAMBC (contained the Ag NPs-OA) and the control cement (plain PMMA cement) was not significant, regardless of the nanoparticles loading of the cement[57]. On Jukrat cells (T-lymphocyte), an experimental AFAMBC (10TPGDA-G1 cement) was significantly less cytotoxic than a counterpart cement (same composition but no TPGDA)[59]. Using a continuous mouse fibroblast cell line (L-929; BS-CL-56), an experimental AFAMBC (Ag-SBA2 cement) was not cytotoxic and the difference in the viability of the cells on the cement and that of its plain counterpart cement was not significant[60].

On human osteoblast (HOb) cells, none of three experimental AFAMBCs (ABC-0.3GO, ABC-15CS, and ABC-0.3GO-15CS cements) showed cytotoxicity because the cellular viability in the presence of extracts taken between 1 d and 7 d increased with time and was > 90%[64]. When HOb was directly seeded on the surfaces of the specimens of each of the AFAMBCs, enhanced surface colonization and proliferation at the early stages (1 and 4 d) was obtained, compared to the case when specimens of plain ABC (control cement) were used[64]. The trends found in this work were also observed when the culture times were 14 d and 21 d[66]. In other words, in each of the AFAMBCs, GO and CS exerted desirable effects on cell adhesion, proliferation, and deposition[66]. These results are consistent with GO increasing the hydrophilicity of the cement surface, thereby allowing easy anchoring of hydroxyl groups to the surface of the cell[86] and the low toxicity of CS and its excellent ability to promote osteoblastic cell growth[87]. After cement immersion for 1 wk, PMMA-NAC cement with NAC loading about 30% wt/vol was significantly less toxic to human fibroblasts, human osteoblasts, and chondrocytes than was the case with control cement (an approved plain cement brand)[67].

The viability of periodontal ligament cells after 7 d of culture on BC-BGII-0.4-AgNP cement was significantly less than on control cement (an approved plain cement brand), with the same trend found for BC-BG-MP-AgNp cement[68]. In general, the results showed that the cytocompatibility of the BC-modified cement is a complex phenomenon, with relevant factors including, but not limited to, the amount of MMA released by a cement, bioactivity of the cement, and amount of BG[68].

Summary of antimicrobial activity and cytotoxicity/cytocompatibility results

The results of the studies summarized in the preceding two sub-sections provide ample evidence that, against micro-organisms that have been commonly found in PJI cases, an AFAMBC has excellent antimicrobial activity and is not cytotoxic and, by extension, has excellent biocompatibility and bioadherence. The first two mentioned characteristics translate to achievement of antimicrobial efficacy being achieved with a very small amount of an AFAMBC. The last-mentioned characteristics indicate that an AFAMBC limits the adherence of planktonic-forming bacteria on an implant surface, which is the first step in biofilm formation[82,83].

Other cement properties

The number of studies in which other cement properties were determined varied widely, from fewer than 5 (example properties: tensile modulus, tensile strength, fracture toughness, and radiopacity) to more than 20 (property: compressive strength) (Table 1). Among these results, there is clear evidence that for an AFAMBC, its maximum polymerization temperature is lower (which is desirable, because it lowers the potential for thermal necrosis of periprosthetic tissue), setting time is longer (which is not desirable, because it increases TJA surgery time), compressive strength and flexural modulus are each comparable (both of which indicate that the load-bearing ability of an implant anchored using either an ALBC or an AFAMBC would be comparable) and cell viability is higher (which is desirable because it indicates increased cell survival in the presence of an AFAMBC), relative to corresponding values for the control cement (which, in all but two studies, was a plain cement, that is one in which there was no antimicrobial additive). However, the trend in each of the other cement properties determined is unclear.

CRITICAL APPRAISAL OF THE LITERATURE

With reference to clinically-relevant properties other than those discussed in the previous Section, the literature has a few attractive features but many shortcomings.

Attractive features

First, the surfaces of specimens of formulated AFAMBCs have been extensively characterized, using an assortment of methods, such as scanning electron microscopy without and with energy dispersion spectroscopy[52,55,58-60,62-66], transmission electron microscopy[54], x-ray diffraction[55], Fourier transform infrared spectroscopy[58,59,64,65], x-ray photoelectron spectroscopy[58], atomic force microscopy[57,64], and Raman spectroscopy[64]. One noteworthy result from these characterization studies is that distribution of the GO in a GO-based AFAMBC, obtained using Raman mapping, showed that GO is well distributed within the cement matrix[64], which, it was suggested, will enhance mechanical properties of the AFAMBC[64].

Second, the literature contains a large assortment of *in vitro* properties of the formulated ALAMBCs, ranging from release of the antimicrobial agent and its activity against *S. aureus* to cytocompatibility against human osteoblast cell line and water uptake. In this regard, the studies by Prokopovich *et al*[57] and by Russo *et al*[61] merit special mention because their studies illuminate subtle differences in the mechanical behavior of AFABCs and their control cement counterparts. In the Prokopovich *et al*[57] study, near-surface values of elastic modulus were determined using a quasi-static nanoindentation technique (atomic force microscopy). One key finding was that for specimens conditioned in PBS, at 37 °C, for 4 wk before the test, the elastic moduli at the surface and the bulk of a specimen were about the same, regardless of whether the cement was an AFAMBC or its control cement counterpart (no antibacterial agent added). Russo *et al*[61] performed small punch tests on miniature disk-shaped cement specimens. The load-displacement curves obtained displayed an initial linear zone, followed by a decrease in slope, achievement of a peak load (P_{peak}), and, finally, a drop in load until fracture occurs. The results showed that P_{peak} for an AFAMBC with low loading (0.25% Au NPs) was significantly higher than that of the control cement but, with an AFAMBC that has a higher loading (0.5% and 1.0% Au NPs), P_{peak} was lower than that of the control cement. These results are consistent with the postulate that with high Au NP loading, either NP clusters form, which act as weak features, and/or a different ductility exists between the cement matrix and the Au NPs, which acts to weaken the cement by creating stress risers and discontinuities at the matrix-Au NPs interface[61].

Third, in a few studies, an additive used to formulate an AFAMBC bestowed an additional benefit of bioactivity to the cement. Lack of bioactivity (and, hence, poor osseointegration) is one of the shortcomings of ALBCs[20]. The aforementioned additives were the powder of a bioactive glass, chitosan, and graphene oxide nanosheets[55,60,62-66]. After 7-28 d of immersion of specimens of bioactive glass powder-loaded cement in simulated body fluid, at 37 °C, there was evidence of agglomerates on the specimen surface that were rich in calcium and phosphorus (hydroxyapaptite (HaP)) (Ca/P ratio = approximately 0.9 to approximately 4.0)[60,62,63]. Among other actions, Ca and P ions combine with local ions to form a HaP-like layer on the surface of components of a TJA, which enhances the ability of the surface to bond with both soft and hard tissues[88]. Furthermore, these agglomerates exhibited the globular morphology that was typical of HaP grown on the surfaces of biomaterial specimens[60,62,63].

Shortcomings

First, with only two exceptions[51,53], an ALBC was not used as the control cement in the studies. This means that comments cannot be made on the potential for AFAMBCs to replace ALBCs in clinical practice.

Table 1 Key trends[a] in a selection of properties of antibiotic-free antimicrobial poly (methyl methacrylate) bone cements

Property	Loaded additive[b] in AFAMBC formulation	Magnitude of trend[c]	Ref.
Tensile modulus	15%CS; 15% CS NP; 15% QCS NP; 10% QAMA; 5% TPGDA G1.0	↓; approximately; approximately; approximately; approximately	Shi *et al*[51]; Shi *et al*[51]; Shi *et al*[51]; Deb *et al*[52]; Abid *et al*[59]
Tensile strength	10% QAMA; 5% TPGDA G1.0	approximately; approximately	Deb *et al*[52]; Abid *et al*[59]
Compressive modulus	0.5% Ag NP; 5% TPGDA G1.0; 0.25% Au NP	↓; ↓; approximately	Slane *et al*[58]; Abid *et al*[59]; Russo *et al*[61]
Compressive strength	10% QAMA; 1% Ag-TIOP NP; 30% SBAG; 7% PP NP; 0.05% Ag-OA NP; 0.5% Ag NP; 5% TPGDA G1.0; 0.25% Au NP; 10% Cu-SBA3 NP; 0.3% GO; 15% CS; 0.3% GO-15% CS	approximately; approximately; approximately; approximately; approximately; ↓; approximately; approximately; approximately; approximately; ↓; ↓	Deb *et al*[52]; Prokopovich *et al*[54]; Miola *et al*[55]; Perni *et al*[56]; Prokopovich *et al*[57]; Slane *et al*[58]; Abid *et al*[59]; Russo *et al*[61]; Miola *et al*[62]; Zapata *et al*[64,66]; Zapata *et al*[64,66]; Zapata *et al*[64,66]
Flexural modulus	CS; CS NP; QCS NP; 0.5% Ag NP; 20% Ag-SBA2 NP; 10-50% NAC; 0.3% GO; 15% CS; 0.3% GO-15% CS	↓; approximately; approximately; approximately; approximately; ↓; approximately; ↓; ↓	Shi *et al*[51]; Shi *et al*[51]; Shi *et al*[51]; Slane *et al*[58]; Verne *et al*[63]; Sukhonthamarn *et al*[67]; Zapata *et al*[66]; Zapata *et al*[66]; Zapata *et al*[66]
Flexural strength	0.5% Ag NP; 20% Ag-SBA2 NP; 10-50% NAC; 0.3% GO; 15% CS; 0.3% GO-15% CS	approximately; ↓; ↓; approximately; ↓; approximately	Slane *et al*[58]; Verne *et al*[63]; Sukhonthamarn *et al*[67]; Zapata *et al*[66]; Zapata *et al*[66]; Zapata *et al*[66]
Fracture toughness	0.5% Ag NP	approximately	Slane *et al*[58]
Storage modulus and loss; modulus vs. time profile	7% PP NP	approximately	Perni *et al*[56]
Elastic modulus vs. depth	0.05% Ag-OA NP	approximately	Prokopovich *et al*[57]
Maximum polymerization	10% QAMA; 0.3% GO; 15% CS; 0.3% GO-15% CS; BC-BG-MP-Ag NP	↓; approximately; approximately; ↓; approximately	Deb *et al*[52]; Zapata *et al*[66]; Zapata *et al*[66]; Zapata *et al*[66]; Wekwejt *et al*[68]
Setting time	10% QAMA; 0.3% GO; 15% CS; 0.3% GO-15% CS; BC-BG-MP-Ag NP	↑; approximately; ↑; ↑; approximately	Deb *et al*[52]; Zapata *et al*[66]; Zapata *et al*[66]; Zapata *et al*[66]; Wekwejt *et al*[68]
Water contact angle	5% TPGDA G1.0; 10% TPDGA G1.0; 0.1% GO; 0.2% GO; 0.3% GO; 0.5% GO; BC-BGII-0.4-Ag NP; BC-BG-MP-Ag NP	↓; ↓; ↓; ↓; ↓; ↓; ↑; ↑	Abid *et al*[59]; Abid *et al*[59]; Zapata *et al*[65]; Zapata *et al*[65]; Zapata *et al*[65]; Zapata *et al*[65]; Wekwejt *et al*[68]; Wekwejt *et al*[68]
Radiopacity	10% QAMA; 20% Ag-SBA2 NP	approximately; ↑	Deb *et al*[52]; Verné *et al*[63]
Residual monomer content	15% CS; 0.3% GO-15% CS; 0.1% GO; 0.2% GO; 0.3% GO	↑; ↑; approximately; approximately; ↑; ↑	Zapata *et al*[64]; Zapata *et al*[64]; Zapata *et al*[65]; Zapata *et al*[65]; Zapata *et al*[65]; Zapata *et al*[65]
Uptake of PBS, at 37 °C, *vs* test time profile	0.05% Ag-OA NP; 15% CS; 0.3% GO-15% CS	approximately; ↑; ↑	Prokopovich *et al*[57]; Zapata *et al*[64]; Zapata *et al*[64]

[a]Trend is ratio of mean value of property of antibiotic-free antimicrobial poly (methyl methacrylate) bone cement (AFAMBC) to that of a plain counterpart control cement (no antimicrobial additive), except in the study by Shi *et al*[51], in which the counterpart control cement was an approved antibiotic-loaded bone cement.

[b]CS: chitosan.

[c]:↓: Ratio is much less than 1 (mean property value for AFAMBC significantly lower than that for control cement); Approximately: Ratio is about 1 (difference in mean property values not significant); ↑: Ratio is much greater than 1 (mean property value for AFAMBC significantly higher than that for control cement). CS NP: Chitosan nanoparticles; QCS NP: Quaternary ammonium chitosan derivative nanoparticles; QAMA: Quaternary amine dimethacrylate; TPGDA G1.0: Generation-1 tripropylene glycol diacrylate dendrimer; Ag NP: Silver nanoparticles; Au NP: Gold nanoparticles; Ag-TIOP NP: Silver nanoparticles capped with tiopronin; SBAG: Particles of Na_2O-CaO-P_2O_5-B2O_3-Al_2O_3-Ag_2O glass; PP NP: Propylparaben nanoparticles; Ag-OA NP: Silver nanoparticles capped with oleic acid; Cu-SBA3 NP: Powder of copper-doped bioactive glass (48% SiO_2-26% Na_2O-22% CaO-3% P_2O_5-0.43% B_2O_3 -0.57% Al2O3) nanoparticles; GO: Graphene oxide nanosheets; Ag-SBA2 NP: Powder of silver-doped bioactive glass (SiO_2-Na_2O-CaO-P_2O_5- B_2O_3-Al_2O_3) (< 20 mm) nanoparticles; NAC: N-acetylcysteine; BC-BG-MP-Ag NP: A composite cement comprising bone cement, a Bioglass (70 mol%SiO_2/30 mol%CaO), and silver nanoparticles; BC-BGII-Ag NP: A composite cement comprising a Bioglass and silver nanoparticles.

Second, in some studies, the plain cement that was used as the control contained a constituent that is not part of the composition of any approved plain cement brand (or, indeed, any approved ALBC brand); specifically, 2-(diethylamino) ethyl acrylate (DEAEA), and 2-(diethylamino) ethyl methacrylate (DEAEM) in the liquid[64-66].

Third, there was only one study in which, for the preparation of the cement dough, the powder (with or without antimicrobial additive(s)) and the liquid (with or without antimicrobial additive) were mixed under vacuum[50]. In all the other studies, the mixing method was either manual[51,52,54-56,59,64-66,68] or a mechanical mixer was used[62]; or, else, the mixing method used was not explicitly stated[57,60,

61,63,66]. It is well known that mixing method exerts a significant influence on the properties of curing and cured properties of PMMA bone cement[20].

Fourth, in the evaluation of the antimicrobial activity of the cements, a clinical/hospital strain of microorganisms that are commonly found in PJI cases (such as *S. aureus* and *S. epidermidis*) was used in only two studies[50,68]. More importantly, in very few studies was a biofilm utilized in the evaluation of antimicrobial activity of the cements[50,62]. This situation is unfortunate given universal acknowledgement that PJI is a form of biofilm-associated implant-related musculoskeletal infection[34,82,83,89-91]; specifically, there is a "race to the top" in which the released antibiotic is inefficacious if a biofilm forms on the surface of the implant before the released antimicrobial agent gets there[92-94].

Fifth, in only a few studies was a human cell line used in the evaluation of cytotoxicity of the cements [50,52,64-66,68]. To give studies clinical relevance, use of a human cell line is preferred to use of cell lines from animals, such as mouse fibroblast.

Sixth, determination of release of the antimicrobial agent from an AFAMBC was conducted in fewer than 30% of studies [54-57,60,62]. Comparing and contrasting the details of this profile to that from an ALBC counterpart[25] would have provided information that may be useful in the design of future AFAMBCs.

Seventh, *in vivo* evaluation of AFAMBCs have been performed in only two studies. In the first, the cements compared were an approved plain bone cement brand (PBC), two experimental cement formulations (an approved plain bone cement brand loaded with 0.6 or 1.0 wt/wt% Nanosilver) (EAGC)), and an approved ALBC brand (antibiotic: tobramycin) (TOBC)[53]. Into the medullary canal of the right femur of female New Zealand White rabbits was injected a cement dough after contamination with a commercially-available *S. aureus* strain[53]. After 14 d, 100% incidence of *S. aureus* was found in all the rabbits in which either PBC or EAGC used, whereas, when TOBC was used, the incidence was 17% (2 out of the 12 rabbits). These results suggest that EAGC may not be suitable for use in revision TJA, where bacteria are already in the periprosthetic tissues[53]. In the second study[66], a dough of the cement (plain, ABC-0.3GO, ABC-15CS, or ABC-0.3GO-15CS cements) was injected into 5 mm-diameter defect created in the parietal bone of Wistar rats (age and mean mass = 8 mo and 0.37 kg, respectively)[66]. After 3 mo of implantation, higher amounts of osseointegration and biocompatibility were obtained with each of the experimental AFAMBC formulations (ABC-0.3GO, ABC-15CS, and ABC-0.3GO-15CS) compared to the corresponding values when the plain bone cement brand was used[66].

Eighth, the quality of the statistical analysis of results presented in the reports was variable. In four reports, there was no mention that statistical analysis was performed[50,59,60,63] even though, in one of them, it was stated that there was "no significant difference in quantitative cytotoxicity testing between the NanoSilver bone cement and the non-toxic control group"[50]. In the vast majority of studies, a parametric test of comparison (Student *t*-test, or ANOVA) was used for intergroup comparisons[51,52,54-57,61,62,64-66]. In only two reports (those by Slane *et al*[58] and by Wekwejt *et al*[68]**)** was the correct methodology used; that is, test for normality and homogeneity of variance of the datasets was conducted before a parametric test of comparison was applied.

FUTURE PROSPECTS

The shortcomings of the literature, as expounded on in the immediately preceding Section, together with other considerations, lead to identification of potential areas for future research. Four are presented here.

First, detailed studies should be performed on the influence of an AFAMBC on the ability of bacteria to form biofilm on surfaces of alloys currently used to fabricate parts of TJA, such as the stem of a total hip arthroplasty (for example, Ti-6Al-4V and Co-Cr-Mo[95], and those proposed for such use (for example, Ti-34Nb-2Ta-0.5O[96], Ti-12Nb-12Zr-12Sn[97], Ti-13Nb-13Zr[98], 40Ti-60Ta composite[99], Ti-39Nb-6Zr-0.45Al[100], and cold groove-rolled Ti-35Nb-3.75Sn[101]). Specifically, these studies should focus on determining the effectiveness of an AFAMBC vis a vis biofilms; that is, the extent to which an AFAMBC: (1) Inhibits microbial adhesion to the surface and colonization; (2) Interferes with the signal molecules that modulate biofilm formation (and associated increased antibiotic tolerance) (for example, quorum sensing inhibitors and/or quorum quenching agents[102-105]; and (3) Disaggregates the biofilm matrix[89,90,92,93,104-110].

Second, studies should be conducted to determine cement properties that have been the subject of only a few studies, such as radiopacity, fracture toughness, and liquid contact angle (q), or have not been determined, examples being fatigue performance (fatigue life and/or fatigue strength), fatigue crack growth/propagation rate, and creep. With regard to q, it should be determined using a biosimulating solution, such as PBS or simulated body fluid, rather than water, as has been the case[59,68]. Fatigue performance should be determined following the method stipulated in the relevant bone cement testing standard (ASTM F2118 or ISO 16402[111,112]).

Third, there are number of novel antimicrobial materials that should be investigated for their suitability to be formulated into a suitable form to be used as additives for an AFAMBC. Examples of materials that could be added to the powder of a plain cement are a quorum-sensing inhibitor drug

[113], Ti-doped ZnO[114], nano-GO nanosheets[115], selenium nanoparticles[116], Ag-nanoparticle-reduced GO nanocomposite[117], chitosan hybrid nanoparticles[118], a Cu cluster molecule[119], powder prepared from extract from a Tunisian lichen[120], Yb-doped ZnO nanoparticles[121], and an analog of PKZ18 (PKZ18-22), a molecule that has been shown to block growth of antibiotic-resistant *S. aureus* in biofilm[122]. Examples of materials that could be added to the liquid of a plain cement are benzothiazole or one of its derivatives[123,124] and a natural antimicrobial agent (such as extract of *Salvadora persica*, *Olea europaea*, and *Ficus carcia* leaves[125] or biosynthesized ZnO nanoflowers[126]).

Fourth, in all studies, the control cement must be an ALBC, preferably an approved ALBC brand. This will ensure that the results of property determinations will be used as a basis for making a recommendation on the clinical use of an AFAMBC instead of an ALBC.

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MINIREVIEWS

Lateral epicondylitis: New trends and challenges in treatment

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Abstract

Lateral epicondylitis (LE) is a chronic aseptic inflammatory condition caused by repetitive microtrauma and excessive overload of the extensor carpi radialis brevis muscle. This is the most common cause of musculoskeletal pain syndrome in the elbow, inducing significant pain and limitation of the function of the upper limb. It affects approximately 1-3% of the population and is frequently seen in racquet sports and sports associated with functional overload of the elbow, such as tennis, squash, gymnastics, acrobatics, fitness, and weight lifting. Typewriters, artists, musicians, electricians, mechanics, and other professions requiring frequent repetitive movements in the elbow and wrists are also affected. LE is a leading causation for absence from work and lower sport results in athletes. The treatment includes a variety of conservative measures, but if those fail, surgery is indicated. This review summarizes the knowledge about this disease, focusing on risk factors, expected course, prognosis, and conservative and surgical treatment approaches.

Key Words: Diagnosis; Lateral epicondylitis; Tennis elbow; Treatment; Review

Core Tip: Lateral epicondylitis (LE) is the most common cause of musculoskeletal pain in the elbow. LE is a leading causation for absence from work and lower sport results in athletes and has a negative impact on the job and social life of patients. Despite extensive research in the last few decades and the plenty of different articles concerning the causes, pathogenesis, and treatment, LE remains a challenge. In this article, we summarize the knowledge about this condition, emphasizing the risk factors, the development of symptoms and the prognostic value of individual factors, and the treatment approaches.

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INTRODUCTION

Lateral epicondylitis (LE) is the most common cause of musculoskeletal pain in the elbow and is associated with significant pain and severe limitation of upper limb function. This condition is also known as periostitis, tendinitis of extensor carpi radialis brevis muscle (ECRB), epicondyloalgia, radial epicondyliti, *etc*., but is most commonly described in the literature as tennis elbow (TE) or LE[1]. LE could be caused by previous trauma but is mainly associated with overload activities that require repetitive prono-supination of the forearm and full extension of the elbow. Other risk factors include degenerative changes of the tendons and disruption of the local blood supply in the area. Usually, there is no pain at rest, but the so-called "extensor activity" provokes pain. Statistics show that LE mainly targets patients of “active” age and has a negative impact on their job and social life, thus indirectly affecting the economics of the country. Although it has been highly researched in the last few decades and there are many different articles concerning the causes, pathogenesis, and treatment, it still presents a challenge for specialists. The aim of this article is to briefly summarize the existing knowledge about this condition, emphasizing the risk factors, the development of symptoms and the prognostic value of individual factors, as well as different treatment approaches. In this manuscript, we will critically review the available literature, including recent publications, and outline some future prospects for the development of research on LE.

HISTORY OF LE

In 1873, Runge first described LE as a "writer's cramp." The term “tennis elbow” was introduced by Morris in 1882, but it was Momberg in 1910, who first described this condition in detail[2]. In his monograph on TE in 1936, James Cyriax concluded that the natural course of LE is between six months and two years[3]. This statement has been widely accepted by different authors over the years, but currently, it is considered that the symptoms of LE could persist for many years and relapses are very common[4].

In 1979, Nirschl *et al*[5] were the first to present surgical treatment of LE, with 97.7% good and excellent results, and in 85.2% of the cases, patients returned to active sports.

EPIDEMIOLOGY AND RISK FACTORS

LE is a relatively common pathology, affecting between 1%-3% of the population. Approximately 4-7/1000 of the patients visit their general practitioners due to symptoms of LE. It is estimated that approximately 40% of all people show some symptoms of LE throughout their life. An interesting fact is that Sanders *et al*[6], in their population study, observed a significant decrease in the annual incidence of LE in 2000 from 4.5/1000 to 2.4/1000 in 2012. According to them, the lower frequency could be due to either changes in the diagnostic approach or to a real decrease in the LE cases. LE usually affects men and women aged between 30-50, and there is no gender predominance[7]. An interesting fact is that more than 50% of nonprofessional tennis players suffer from this disease, but only 5% of professional tennis players complain of LE. Players in other sports, such as badminton and squash, can also be affected. In athletes, the symptoms are associated with poor backhand performance, low grip of the racket, too tight cord of the racket or in cases when players use wet and heavy balls[8]. LE most commonly affects the dominant hand, especially when performing daily repetitive motions. It is the reason for some of the longest absences from work. Up to 17% of factory workers, as well as meat processors who have repetitive and similar hand movements, suffer from LE. Typists, artists, musicians, electricians, mechanics, and others can also be affected. It is well known that workers involved with repetitive movements of the hands and wrists have an increased risk of LE[9,10], are more resistant to treatment and have a worse prognosis[11,12]. One of the reasons for persistent pain in LE is central sensitization, associated with reduced thresholds of nociception and increased time summation[13]. There is evidence that patients with LE exhibit widespread hyperalgesia, which results in a higher score on the pain scale and prolonged duration of the symptoms. Herquelot *et al*[10] studied the influence of physical and psychological factors on the occurrence of elbow and LE diseases among a group of 3710 workers in France. Elbow pain without LE was reported in 10.5% of the workers, and LE was diagnosed in 2.4% of the workers. Age, body mass index (> 25) and low social support (men only) were significant

risk factors. Heavy exercise combined with repetitive elbow flexion/extension for more than two hours a day and wrist flexion for more than two hours a day were the most significant risk factors for elbow pain and LE.

According to Sanders *et al*[6], the most common professional activities of patients with LE are office workers or secretaries and medical staff, mainly nurses.

In a recently published case–control study of the influence of various factors on the occurrence of LE, Park *et al*[14] found that female sex, dominant hand involvement, manual labor, and ipsilateral rotator cuff rupture were risk factors for LE. The results of the study show that excessive use of the limb is a stronger risk factor for LE than metabolic factors[14].

According to some reports, there could be a link between LE and the use of fluoroquinolones. Such a consequence has been reported in Achilles tendon degeneration[15].

Studies show that LE leads to absences from work for up to 219 working days of the year, with a cost of $8099 per patient. Data from the Workcover Queensland show that diseases affecting the upper limb (shoulder and elbow) accounted for 18% of all occupational diseases from 2009 to 2013, which is equal to the prevalence of diseases in the back[16].

SYMPTOMS, DIAGNOSIS AND EVOLUTION

Clinical examination usually presents with increased sensitivity and pain during palpation in the lateral epicondyle area, which is exacerbated by prono-supination of the forearm. The pathognomonic sign of LE is the test in which pain is provoked by the extension of the wrist against resistance, as well as the "chair back test".

Precise evaluation of the pain should be assessed at the beginning of the symptoms because there is evidence that patients with more severe pain syndrome in the first presence of the disease have a higher potential for persistence of the pain at the twelfth month[17]. The "Patient Rated Tennis Elbow Evaluation" is an LE-specific questionnaire that includes pain and impairment scales that are collected to give an overall score from 0 (no pain or injury) to 100 (strongest pain or injury)[18]. A minimum change of 11 points or 37% of the baseline assessment is considered clinically significant[19]. The most common functional limitation in LE is grip pain, which can be measured as painless grip strength and is a reliable and valid indicator that is more sensitive than measuring maximum grip strength[20]. It is measured with the patient lying, the elbow is in a slight extension and the forearm is in pronation, as the patient squeezes the dynamometer until the first appearance of pain. The final calculation consists of the average of three tests performed at one-minute intervals.

From the imaging tools, the X-ray could exclude other pathological conditions of the elbow, and in rare cases, small calcifications could be observed. Ultrasound can provide more accurate data by visualizing the initial location of the muscle and the possible thickening of the tissues around the tendon as a result of the inflammatory process[21]. The most accurate assessment can be made by magnetic resonance imaging (MRI). It shows thickening of the proximal muscle insertion with increased signal in T1 and T2 presented in 2/3 of patients. These characteristics may persist for a long time after the symptoms have resolved[22]. Ultrasound and MRI are highly sensitive but are nonspecific for proving LE. However, the absence of a pathological finding from these tests can certainly rule out LE. The presence of a large rupture (≥ 6 mm) in the tendon or lateral collateral ligament is a crucial part of the differential diagnosis, as it is associated with unsuccessful conservative treatment[23]. Infrared thermography in 94%-100% of patients with LE shows abnormally increased epicondylar activity around the lateral epicondyle. Isotope testing is also positive in 72% of the patients[24], although these two methods are practically not used routinely.

Electromyography and cervical and thoracic spine examinations could also be helpful in diagnosing the source of pain symptoms in the spine. Although the influence of cervical and thoracic spinal diseases on LE is not fully understood, some studies show that neck pain is more common in people with LE[25]. Moreover, patients with LE who also complain of shoulder or neck pain have a worse prognosis[18].

Current data show that the disease usually develops over the years, with common recurrences. This changes the initial assessment that LE is limited from six months to two years. Over 50% of patients report that elbow pain still persists after 12 mo[26,27]. Follow-up of participants in a clinical trial[4] of nonsurgical treatment of LE showed that 20% of patients (27/134) reported pain after three to five years (3.9 years on average), regardless of treatment regimens, and that those with an initial severe pain syndrome had a 5.5 times higher rate of pain symptoms due to LE. Therefore, LE is considered a nonself-limiting condition and is associated with continuous pain in a large number of patients. Sanders *et al*[6] indicated an 8.5% recurrence rate over two years, and it remained constant over time. The surgically treated cases within two years after diagnosis have increased three times for the period of the study/2001-2012/, from 1.1% for the period between 2000-2002 up to 3.2% after 2009. One of ten patients with persistent symptoms at the sixth month required surgical treatment.

CONSERVATIVE TREATMENT

Conservative treatment of LE includes nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, topical corticosteroid application, rest, cryotherapy, acupuncture, kinesitherapy, physical therapy including ultrasound, iontophoresis, deep transverse frictions, shock wave and lazer therapy, manual therapy, exercises strengthening the muscles, *etc.* Wearing an epicondylar bandage is also a part of conservative treatment[28].

Although there is still no generally approved algorithm for the treatment of LE, it is now accepted that the start of the treatment should be with oral NSAIDs[29]. In the short term, oral NSAIDs affect pain compared to placebo, but there are still no data for the 6- to 12-mo period. There are insufficient data on the efficacy of NSAIDs on pain compared with injectable corticosteroids, but as a global effect on symptoms, NSAIDs have shown lower efficacy. In terms of arm function improvement, NSAID administration did not show a significant improvement compared with placebo[30]. Topical NSAIDs improve pain symptoms, but arm function compared with placebo effects is uncertain[30]. Studies in the treatment of LE have shown a significant improvement in the symptoms of topical corticosteroid injection compared with placebo or NSAIDs. A positive effect is reported in both pain and arm function. There is no comparison of efficacy with different types of corticosteroids[30]. In addition to the corticosteroid, a local anesthetic injection was given. The results of the studies showed an overall improvement in pain symptoms and arm function in both groups, with no significant difference between the groups treated with corticosteroids or anesthetics[31]. Interestingly, there is evidence that corticosteroid injections have a higher recurrence rate after 6 wk in patients with LE than in the placebo group or untreated patients. Additionally, compared with combined physical therapy, corticosteroid injections appear to cause a higher recurrence rate after 6 wk[30].

OTHER CONSERVATIVE TREATMENT OPTIONS

In 2011, Creaney *et al*[32] published the results of a prospective randomized study using growth factors to improve the healing processes of musculoskeletal injuries in sports medicine. It is believed that injecting autologous blood stimulates an inflammatory response, which would prompt healing stimulation. However, the benefit of the method has not been found in long-term follow-up, and its use is recommended only in those cases where other treatment options have failed. Autologous platelet-rich plasma (PRP) is another option used to treat LE. PRP is made by using a sample from the patient's own blood. It is widely used in orthopedics and sports medicine as a method of recovery after various soft tissue injuries or after surgical interventions. PRP is a potential treatment option in patients with LE in cases of physiotherapy failure[33]. Mishra *et al*[34] reported the results after PRP in a prospective cohort study in 230 patients who did not respond to at least three months of conservative treatment for LE. At 24 wk, PRP injection resulted in a significant improvement in pain compared to the control group (71.5% *vs* 56.1%, $P = 0.019$), as well as a significantly lower percentage of patients reporting residual sensitivity in the elbow area (29.1% *vs* 54.0%, $P = 0.009$). A study by Shim *et al*[35] found no difference between PRP administration and own blood injection. However, the significant differences between the various PRP systems and the different techniques used in producing them complicate the comparison of the results of the various studies[33]. Leukocyte concentration affects the quality of PRP. New data suggest that leukocyte-rich PRP may provide pain relief and good outcomes for LE patients compared to alternative topical injections. Additionally, better results are seen with the use of leukocyte-rich PRP than with the use of leukocyte-poor PRP[35]. In a pilot study of 12 patients with refractory LE, Connell *et al*[36] showed that collagen-producing tenocyte-like cells derived from autologous skin fibroblasts that were injected with a PRP-rich matrix led to clinical and ultrasound improvement. In 2013, Wang *et al*[37] published the results of a study on the use of autologous tenocytes derived from patellar tendon cells and injected under ultrasound control for the treatment of severe refractory LE in 16 patients. These cells are preferred because of their potential for collagen synthesis and rapid proliferation.

Botulinum toxin A has also been proposed for the treatment of LE. In 1997, Morré *et al*[38] first described its use in LE. The authors suggest that botulinum toxin injections could aid in the treatment of LE by causing reversible paresis of the extensors, especially m. ECRB, thus preventing the development of microtraumas in its proximal insertion. Placzek *et al*[39] conducted a multicenter randomized controlled trial in which 130 patients were treated with botulinum toxin or placebo. Patients treated with botulinum showed significant improvements in pain measured by the analog scale at the 6th, 12th, and 18th weeks. However, the application could provoke weakness in the wrist extensors and reduced grip strength. Regardless of the results obtained from these studies, Hayton *et al*[40] failed to prove a significant difference between the Botox-treated group and the control group.

PHYSICAL THERAPY

Physiotherapy and kinesitherapy play a significant role in the treatment of TE. Their use could start in the acute phase or immediately after diagnosis to reduce pain and continue in the early and late postoperative period to restore range of motion, joint function, recovery of muscle strength and prevention of contractures. In the different stages, specific combinations of the above-described methods could be used by preparing individual rehabilitation programs.

Different combinations of exercises have also been used for the treatment. They are usually part of a complex treatment. Despite controversial results, there is evidence from several randomized controlled trials that exercise may be more effective in reducing pain and improving arm function than other procedures, such as ultrasound, placebo ultrasound and manual therapy, but there is no difference in muscle strength and function between various types of exercises[30,41,42]. Manual therapy for the elbow, wrist and cervicothoracic spine can reduce pain and increase the strength of the pain-free grip immediately after treatment. Unfortunately, meta-analysis is not possible due to heterogeneity between manual therapy techniques and follow-up time. There is insufficient evidence of the long-term clinical effects of manual therapy alone in LE[43-47].

The use of ortheses is another popular LE treatment option. The variety of different orthotic devices and the different follow-up methods for evaluating their effectiveness makes it difficult to analyze the published data. Overall, there is generally controversial evidence for the effectiveness of orthoses as an improved method for arm function and pain relief compared to placebo or in untreated patients. There is no evidence of the superiority of one type of orthosis over others[48-52].

Topical application of ice is a traditional method for pain management. However, evidence for its effectiveness in LE is limited. In a controlled clinical trial, Manias *et al*[53] failed to demonstrate the advantage of using ice in combination with exercise over using exercise alone.

Acupuncture is used in the treatment of many musculoskeletal disorders, and LE is no exception. After reviewing the literature on the subject, Trinh *et al*[54] concluded that acupuncture is effective in relieving complaints in the short term. Acupuncture is shown to be more effective in relieving pain and improving function than ultrasound, both at the end of the treatment and at the six-month follow-up [55].

The use of laser therapy in LE is effective in the short term compared to placebo, but in the long term, however, no advantages are found compared to other physical methods. Lasers with a wavelength other than 904 nm did not show better efficacy than placebo[56-58]. The analysis of data from clinical trials on the effect of ultrasound therapy and iontophoresis in LE shows that they do not have an advantage over the use of placebo[30]. The data for the application of shock-wave therapy are similar and are not more effective than placebo or other physical methods[59].

Recently, published data from a meta-analysis show that in the conservative treatment of LE, electrophysiotherapy and physiotherapy should be given priority over other interventions[60].

SURGICAL TREATMENT

Usually, most patients respond to conservative treatment. Nonetheless, in some patients, the symptoms persist for a long time despite treatment. In such cases, a surgical approach is indicated. There are many surgical techniques (Figure 1 and 2), and most of them include debridement of the affected tendon of the m. ECRB and decortication of the lateral epicondyle. Surgery can be performed using open, percutaneous, or arthroscopic techniques.

Open surgery

In 1979, Nirshl *et al*[5] published an operative technique for the treatment of LE, which involved excision of all visibly damaged parts in the area of the insertion of the ECRB muscle. The authors reported an improvement in 97.7% of the patients after surgery. In 2008, Dunn *et al*[61] applied the Nirshl technique in 139 elbows and reported improvement in 97% of them. Numerous surgical techniques have been described in the literature: Excision of the painful area and ablation of the common extensor origin according to Garden; Hohmann surgery in which the initial attachment sites of the extensors are released from the lateral epicondyle; and Kaplan denervation of the humeroradial joint. The most popular technique is that of Boyd and McLeod, which eliminates all possible causes of the disease. It involves excision of the proximal part of the annular ligament, releasement of the insertion of the extensors, excision of the bursa in the area and excision of the synovium of the humeroradial joint. There is no evidence of an advantage of any of the open techniques for the treatment of LE over the others[30].

Percutaneous technique

In 1962, Loose performed a percutaneous technique for releasement of the proximal insertion of the ECRB with local anesthesia for the first time. Good results after percutaneous releasement have also been reported by different authors[62-65]. This procedure is effective in pain relief, uses a minimally

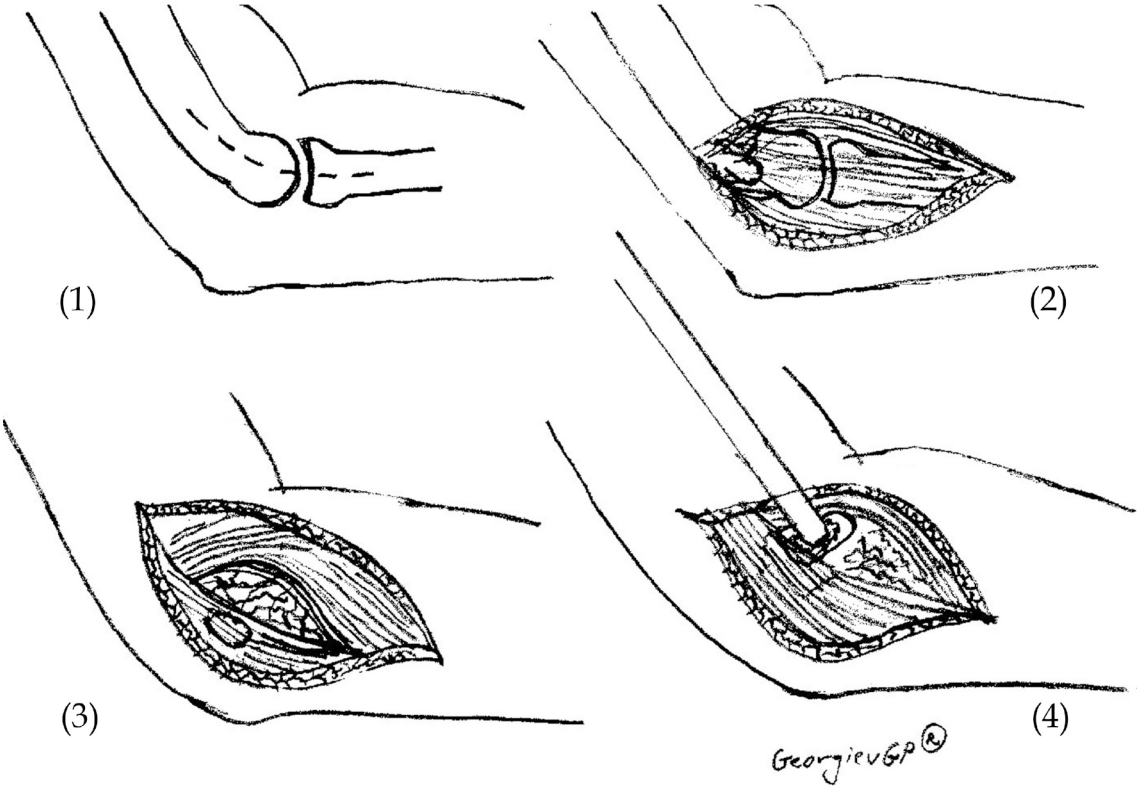

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Figure 1 Scheme presenting the open release of lateral epicondylitis. (1) Skin incision; (2) Extensor carpi radialis longus – extensor digitorum communis interface is identified; (3) Degenerated tissue at extensor carpi radialis brevis muscle is identified and incised; and (4) Osteotome decortication.

invasive approach and can be performed as a one-day surgery. However, the application of percutaneous operative techniques is still controversial. Recently, data on a new percutaneous technique called ultrasound guided percutaneous tenotomy (UGPT) have been published. It is safe and secure and leads to improvement of pain symptoms, hand function and ultrasound imaging at the one-year follow-up[66]. This new surgical technique is applied through an incision of five millimeters using ultrasound energy to remove damaged tissue and cause an inflammatory reaction that promotes the healing process in the tendon[67]. The technique requires the use of special equipment - the TX1 Tissue Removal System (Tenex Health, Lake Forest, CA). Seng *et al*[68] administered UGPT *via* the TX1 Tissue Removal System to a group of 20 patients with refractory LE, reporting improvement in arm function and pain relief after 3 years of follow-up. Boden *et al*[69] compared the results after treatment with PRP or UGPT in patients with medial or LE. No statistically significant difference was found between the two techniques. The authors conclude that both techniques are effective in the treatment of epicondylitis and lead to pain relief and improved arm function and quality of life.

Arthroscopic technique

Arthroscopic surgery is becoming increasingly popular in treating LE in the United States. This procedure involves arthroscopic release of the tendon of the ECRB. The potential benefit of arthroscopic surgery is a shorter recovery time and a better tolerance of the patient. The results of this technique have been reported mainly in a series of patients with positive results. Baker *et al*[70] were the first to apply arthroscopic operative techniques in LE treatment. In arthroscopic surgery, debridement of the pathological tissue is performed. The authors reported good results in 30 patients[71]. Jerosch *et al*[72] also reported good results from arthroscopic treatment in Germany. Currently, a prospective, single-center, double-blind, randomized, controlled study of the efficacy of arthroscopic release of ECRB in patients with LE is conducted[73]. The expected results will allow optimization of the therapeutic approach in patients with LE with a high degree of reliability.

LIMITATIONS AND FUTURE SCOPE

In this review, we used only English language sources from medical databases. It is worth mentioning here that some of the studies included in this literature review are gaining small sample sizes, which increases the likelihood of a type II error. There are significant methodological differences in the design

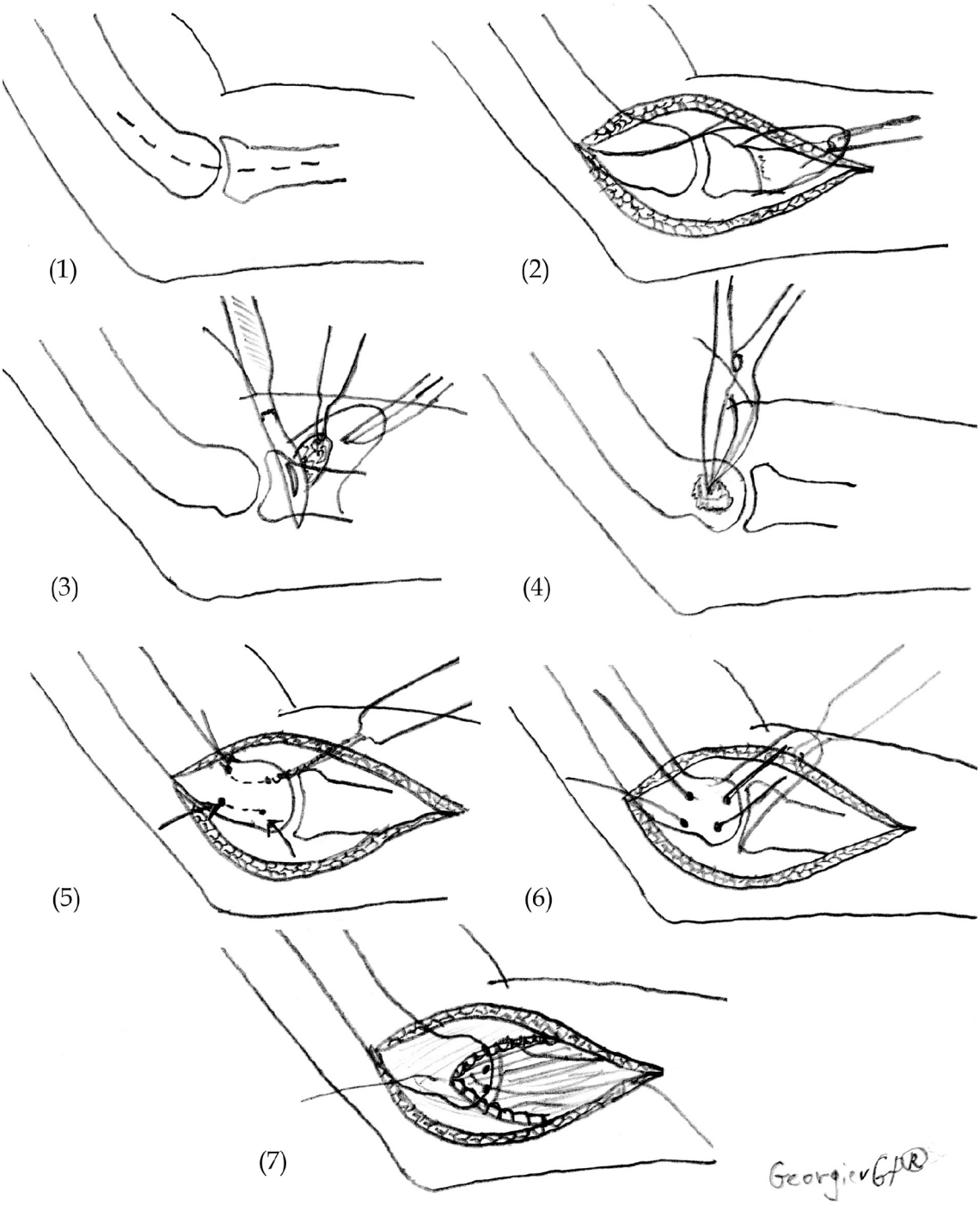

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Figure 2 Scheme presenting the technique for the surgical treatment of lateral epicondylitis. (1) Skin incision; (2) Reflection in the distal direction of the extensor mechanism; (3) Excision of pathologic tissue under the flap of the extensor mechanism; (4) Osteotome decortication; (5) Drilling of two V-shaped tunnels for reattachment of the extensors; (6) Reattachment of the extensor mechanism to the lateral epicondyle; and (7) Restoration of the extensor tendon mechanism.

of the studies between the different studies. In addition, we see a great variety in the methods used to evaluate the results, which means that meaningful data synthesis, which may counteract some of the limitations of individual studies, is difficult.

Although LE has been a known disease for centuries and numerous studies have been conducted on it, there is still a wide horizon for future research and supplementation of our knowledge regarding this disease. First, it is necessary to study in depth the importance of risk factors in light of developing strategies for primary prevention. Another promising area is the study and application of imaging methods using artificial intelligence, which are already entering medical practice[74-76]. Additionally, nonsurgical treatment using various cellular derivatives is a promising therapeutic method[77]. In the near future, we expect to improve the existing methods and introduce new minimally invasive methods of treatment. Researchers' efforts will also focus on establishing an effective therapeutic strategy for

patients with recurrent LE.

CONCLUSION

LE is a common musculoskeletal disorder caused by chronic repetitive overload of the proximal insertion of the extensor carpi radialis brevis muscle that results in local microinjuries, which heal partially and thus induce aseptic inflammation, swelling and pain. Without adequate treatment, this disease could become chronic and lead to significant limitations in daily activities and quality of life impairment. Knowing the nature of this disease is a prerequisite for the implementation of correct therapeutic strategies and therefore achieves a good therapeutic approach and positive results.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Is it necessary to fuse to the pelvis when correcting scoliosis in cerebral palsy?

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Abstract

BACKGROUND

Neuromuscular scoliosis is commonly associated with a large pelvic obliquity. Scoliosis in children with cerebral palsy is most commonly managed with posterior spinal instrumentation and fusion. While consensus is reached regarding the proximal starting point of fusion, controversy exists as to whether the distal level of spinal fusion should include the pelvis to correct the pelvic obliquity.

AIM

To assess the role of pelvic fusion in posterior spinal instrumentation and fusion, particularly it impact on pelvic obliquity correction, and to assess if the rate of complications differed as a function of pelvic fusion.

METHODS

This was a retrospective, cohort study in which we reviewed the medical records of children with cerebral palsy scoliosis treated with posterior instrumentation and fusion at a single institution. Minimum follow-up was six months. Patients were stratified into two groups: Those who were fused to the pelvis and those fused to L4/L5. The major outcomes were complications and radiographic parameters. The former were stratified into major and minor complications, and the latter consisted of preoperative and final Cobb angles, L5-S1 tilt and pelvic obliquity.

RESULTS

The study included 47 patients. The correction of the L5 tilt was 60% in patients fused to the pelvis and 67% in patients fused to L4/L5 (P = 0.22). The pelvic obliquity was corrected by 43% and 36% in each group, respectively (P = 0.12).

Regarding complications, patients fused to the pelvis had more total complications as compared to the other group (63.0% *vs* 30%, respectively, P = 0.025). After adjusting for differences in radiographic parameters (lumbar curve, L5 tilt, and pelvic obliquity), these patients had a 79% increased chance of developing complications (Relative risk = 1.79; 95%CI: 1.011-3.41).

CONCLUSION

Including the pelvis in the distal level of fusion for cerebral palsy scoliosis places patients at an increased risk of postoperative complications. The added value that pelvic fusion offers in terms of correcting pelvic obliquity is not clear, as these patients had similar percent correction of their pelvic obliquity and L5 tilt compared to children whose fusion was stopped at L4/L5. Therefore, in a select patient population, spinal fusion can be stopped at the distal lumbar levels without adversely affecting the surgical outcomes.

Key Words: Cerebral palsy; Scoliosis; Pelvic fusion; Pelvic obliquity; Spinal fusion; Distal lumbar level

Core Tip: The value of including the pelvis in the distal level of fusion in children with cerebral palsy scoliosis is not clear with respect to correcting pelvic obliquity or L5 tilt. This does, however, increase the risk of complications. After careful patient selection, spinal fusion can be stopped at the distal lumbar levels without adversely affecting the surgical outcomes.

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INTRODUCTION

Patients with neuromuscular scoliosis may benefit from surgery with improved standing balance, sitting positioning, and overall better caregiver satisfaction[1]. However, these surgeries are challenging due to severe deformity and presence of comorbidities. Complications are high (20% to 40%) compared to adolescent idiopathic scoliosis (5% to 23%)[2-5]. Posterior spinal instrumentation and fusion is the most common procedure performed. Proximally, fusion is begun T1 or T2 to prevent the development of proximal junctional kyphosis (PJK) which can lead to pain and neurologic deficits[6,7]. The distal extent of the fusion, however, remains controversial. Neuromuscular scoliosis is commonly characterized by pelvic obliquity which affects sitting balance and the development of iliac ulcers[8]. There is debate as to whether pelvic fixation is necessary to correct pelvic obliquity with some authors advocating that those with pelvic obliquity less than 10°-15° do not require fixation to the pelvis[6-8]. The majority of authors, however, advocate for fusion to the pelvis to not only correct the pelvic obliquity but also decrease the risk of distal curve progression and revision surgery[9-11].

The studies that discuss pelvic fusion either focus on children with flaccid forms of paralysis or include a pooled patient cohort including both spastic and flaccid disorders[9-13]. Since these neuromuscular disorders have varying levels of pelvic obliquity and do not necessarily act the same way, we sought to analyze our patients with cerebral palsy (CP) with regards to radiographic outcomes and complications as a function of fusion to the pelvis compared with higher levels of fusion.

MATERIALS AND METHODS

Following institutional review board approval, we retrospectively reviewed our electronic medical records. Surgically treated CP scoliosis patients who had gross motor function classification system levels IV or V and were less than 21 years of age were included. Exclusion criteria were surgery for predominant kyphosis, follow-up less than six months, or incomplete charts. The analysis spanned records from 2007 to 2018 at a single institution. We excluded patients with other indications for surgery, patients with unavailable radiographs, and those with follow-up less than six months. Demographic information, operative details, and the development of complications were recorded. We stratified complications into major and minor as previously described.[14] Major complications were those that prolonged the duration of hospitalization or required additional surgical procedures. These

included severe pulmonary complications (pneumonia, respiratory failure), deep surgical site infections (SSI), hemodynamic instability, pseudarthrosis, and PJK. Minor complications were those that were asymptomatic, self-resolving, or effectively treated non-surgically. Examples include intraoperative durotomy, fever occurring more than 24 h after surgery, decubitus ulcers, superficial SSIs, and superficial wound dehiscence. Pre-operative and final follow up radiographs were measured and Cobb angles, L5-S1 tilt and pelvic obliquity using the Maloney method were recorded[14-17].

Statistical analysis was performed using the IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA). *T*-tests and χ^2 tests were used when appropriate. The relative risk (RR) and 95%CI were calculated to assess whether the fusion level affected the risk of developing postoperative complications. *P* values ≤ 0.05 were considered statistically significant.

RESULTS

Over the study period, 65 children with CP had surgery for scoliosis at our hospital. We excluded 18 cases: 3 had predominant kyphosis rather than scoliosis, 8 had unavailable radiographs, and 7 were lost to follow-up. Our analysis therefore included 47 patients. These were 29 males and 18 females, with an average age of 13.9 years (range: 9.6–19.9 years). All procedures were posterior spinal fusion and instrumentation. The median number of fused vertebrae was 16 (range: 14-17), and 27 patients (57.4%) were fused to the pelvis. Median follow-up duration was 31 mo (range: 7–101 mo).

Patients fused to the pelvis and those fused to L4/L5 were similar with regards to their age, sex distribution, weight, follow-up, and comorbidities. The one exception was that fewer patients fused to the pelvis had seizures. Patient details are included in Table 1. The operative duration and blood loss were not different between both groups. Length of stay was also similar in both groups and was six days on average. With respect to pre-operative radiographic parameters, patients fused to the pelvis had a larger lumbar curve by 17˚ (P = 0.017), greater L5 tilt by 4˚ (P = 0.04), and greater pelvic obliquity by 10˚ (P = 0.0033). The thoracic curve magnitude was similar in both groups (P = 0.17). Table 2 includes the radiographic parameters immediately before surgery and at final follow-up. At the final follow-up, patients who were fused to the pelvis had their thoracic curve corrected by 53%, and their lumbar curve corrected by 38%. Corrections of their L5 tilt and pelvic obliquity were 60% and 43%, respectively. Patients who were fused to L4/L5 had 43% correction of their thoracic curve, 64% of their lumbar curve, 67% of their L5 tilt, and 36% of the pelvic obliquity. The degree of correction of the L5 tilt and pelvic obliquity was similar regardless of fusing to the pelvis (P = 0.22 and 0.12, respectively).

Pelvic obliquity of 10˚ is considered by some to be the threshold for pelvic fusion[6]. Twenty-one of 27 patients fused to the pelvis exceeded this threshold, with a mean of 25˚ (range: 11˚-59˚). This was corrected by 40% to 15˚ (range: 2˚-34˚). In the L4/L5 group, 10 of 20 also had a pelvic obliquity greater than 10˚, with an average of 18˚ (range: 11˚-30˚). Their pelvic obliquity was corrected by 44%, from a mean of 18˚ (range: 11˚–30˚) to 10˚ (range: 4˚-20˚). The magnitude of pelvic obliquity correction was clinically and statistically similar in both groups (P = 0.12). Table 3 stratifies patients according to their preoperative and final pelvic obliquity, and Figure 1 is sample cases of patients who were fused short of the pelvis or whose fusion included the pelvis, respectively.

The complications encountered are detailed in Table 4. The most frequent complications were pulmonary complications (14.9%), pressure ulcers (12.8%), and instrumentation (8.5%). No postoperative neurological deficits or deaths occurred. Two patients underwent reoperation for deep SSI and PJK. Both had been fused to the pelvis. Also two patients had hardware break and one had instrumentation prominence, but all were asymptomatic and were simply observed. Patients with fusion to the pelvis had more total complications (63.0% *vs* 30%, P = 0.025; RR = 2.099; 95%CI: 1.012–4.35, P = 0.046). Their RR for minor complications was 2.41 (95%CI: 0.92–6.29, P = 0.073) and for major complications was 1.48 (95%CI: 0.30–7.31, P = 0.63). Even after adjusting for the differences in radiographic parameters (lumbar curve, L5 tilt, and pelvic obliquity), the risk for complications remained increased (RR = 1.79; 95%CI: 1.011–3.41).

DISCUSSION

Children with CP scoliosis frequently have pelvic obliquity that affects their sitting balance and interferes with transfers. To correct pelvic obliquity and reduce risk of distal adding on, fusion to the pelvis is often recommended[1,10]. Pelvic fusion, however, can lead to surgical morbidity and complications[11,18]. In this study, we compare outcomes in children with CP scoliosis with regards to the distal extent of spine fusion. Pelvic fusion did not increase the operative time or blood loss compared to higher levels of fusion. Published studies have differed, with some demonstrating longer surgeries and more blood loss with pelvic fixation, while other studies did not find a difference[13,19-21]. The long duration of surgery and magnitude of blood loss along with case to case variation may make it difficult to detect differences with statistical significance.

Table 1 Characteristics of patients with cerebral palsy scoliosis

Characteristics	Fusion to pelvis (*n* = 27)	Fusion to L4/L5 (*n* = 20)	*P* value
Demographics			
Average age (yr)	14.2	13.4	0.303
Sex, number of males	19	13	0.52
Average weight (kg)	34.2	35.6	0.66
Average follow-up (mo)	41.7	31.0	0.11
Gastrostomy (*n*)	15	6	0.061
VP shunt (*n*)	4	3	0.95
Seizures (*n*)	10[a]	14[a]	0.050
Operative details			
Average operative duration (min)	341	334	0.72
Average blood loss (mL)	989	1049	0.74

[a]$P \leq 0.05$, between the groups.
VP shunt: Ventriculoperitoneal shunt.

Table 2 Radiographic parameters

	Pre-operative values, mean (Range)	Final values, mean (Range)
Fusion to pelvis		
Thoracic curve (degrees)	30 (0–64)	14 (0-38)
Lumbar curve (degrees)	56 (4–106)	32 (0-68)
L5 tilt (degrees)	10 (0-41)	4 (0-16)
Pelvic obliquity (degrees)	21 (1-59)	12 (0-34)
Fusion to L4/L5		
Thoracic curve (degrees)	42 (2-109)	24 (1-88)
Lumbar curve (degrees)	39 (5-75)	14 (1-47)
L5 tilt (degrees)	6 (0-13)	2 (0-8)
Pelvic obliquity (degrees)	11 (1-30)	7 (2-20)

Table 3 Preoperative and final pelvic obliquity of patients

	Pelvic obliquity		
	< 10°	10°-15°	> 15°
Fusion to pelvis			
Preoperative	6	6	15
Final	12	6	9
Fusion to L4/L5			
Preoperative	10	5	5
Final	15	1	4

We did find differences in complication rates. In our cohort, children fused to the pelvis had an increased risk to develop post-operative complications, with a RR of 2.099, mainly attributable to higher occurrences of minor complications, most notably pressure ulcers and hardware complications. Pelvic fusion leads to a more rigid seating position[1]. In patients with limited mobility, this could increase

Table 4 Complications encountered in both groups, *n* (%)

Complications	Fusion to pelvis (*n* = 27)	Fusion to L4/L5 (*n* = 20)	Total (*n* = 47)
Pulmonary complications			
Respiratory failure[1]	1 (3.7)	1 (5)	2 (4.2)
Atelectasis	3 (11.1)	1 (5)	4 (8.5)
Pneumonia[1]	0	1(5)	1 (2.1)
Pressure ulcer	5 (18.5)	1 (5)	6 (12.8)
Instrumentation			
Hardware break or prominence	3 (11.1)	0	3 (6.4)
PJK[1]	1 (3.7)	0	1 (2.1)
Superficial SSI	0	2 (10)	2 (4.2)
Deep SSI[1]	1 (3.7)	0	1 (2.1)
Wound dehiscence	1 (3.7)	0	1 (2.1)
SIRS[1]	1 (3.7)	0	1 (2.1)
Durotomy	1 (3.7)	0	1 (2.1)
Total	17 (63)	6 (30)	23 (49.9)

[1]Major complications.
SIRS: Systemic inflammatory response syndrome; SSI: Surgical site infection; PJK: Proximal junctional kyphosis.

their risk for decubitus ulcers. We only had few occurrences of SSIs and wound complications, but they are also an important consideration. Deep SSIs are a common cause for reoperation which puts patients at repeated risks of anesthetic complications, bleeding, and injury due to reinstrumentation. This is particularly important in patients with GMFCS levels IV and V, who have significant co-morbidities, are frequently malnourished, and are at increased risk for abnormal wound healing and infections. Again, published reports have conflicting results. Toll *et al*[14] in their evaluation of risk factors following scoliosis surgery in neuromuscular patients did not find that fusion to the pelvis was a risk factor for complications. On the other hand, other studies found an increased risk[22,23]. One possible explanation of this discrepancy is the heterogeneity of the reports which include different neuromuscular conditions in the same analysis.

The two most commonly used determinants for including the pelvis in the fusion are L5 stability and pelvic obliquity. The L5-sacrum articulation is considered stable when the L5 tilt is less than 15°, and it is considered unstable when it is greater than 15°. Fusion to the pelvis is also recommended for pelvic obliquity greater than 10°. In our cohort, even though decision making was not standardized, all patients with a large L5 tilt were fused to the pelvis. However, not all patients with pelvic tilt were fused to the pelvis. The pelvic fusion did have greater L5 tilt and pelvic obliquity than patients fused to L4/L5. Interestingly, the degree of correction of both parameters was similar in both groups. The L5 tilt was corrected by 60% with pelvic fusion and by 67% with fusion to L4/L5 (P = 0.22). Similarly, the pelvic obliquity was corrected by 43% and 36% in each group, respectively (P = 0.12), so fusing to the pelvis did not offer a significantly greater correction of pelvic obliquity. This was also true for the subset of patients with a pelvic obliquity greater than 10°. In this population, correction of pelvic obliquity was 40% for patients fused to the pelvis and 44% for those fused to L4/L5, indicating that even with patients who have a large pelvic tilt, fusion to the pelvis does not necessarily achieve better pelvic obliquity correction. Therefore, a large pelvic obliquity by itself might not be an indication to include the pelvis in the distal extent of the spinal fusion, particularly since these patients experience more complications. Furthermore, fusion to the pelvis may not be necessary in all children with CP scoliosis. This could still lead to satisfactory surgical outcomes including pelvic tilt while decreasing the risk of postoperative complications. Future studies can better delineate selection criteria regarding whether to fuse to the pelvis or not in these children.

Our study has several limitations. As a retrospective study, information was gathered from the medical records, which might lead to some inaccuracies. We aimed to have a homogenous cohort, so we only included children with CP, making our sample size moderate. This made the study underpowered to detect differences at the level of individual complications, but did allow identification of higher total complication rate. Sagittal plane deformities were not assessed. There were no predetermined selection criteria for choosing distal fusion level to the pelvis. Although traditional criteria for fusion to the pelvis were not strictly followed, patients who were fused to the pelvis had more pelvic and L5 tilt, indicating

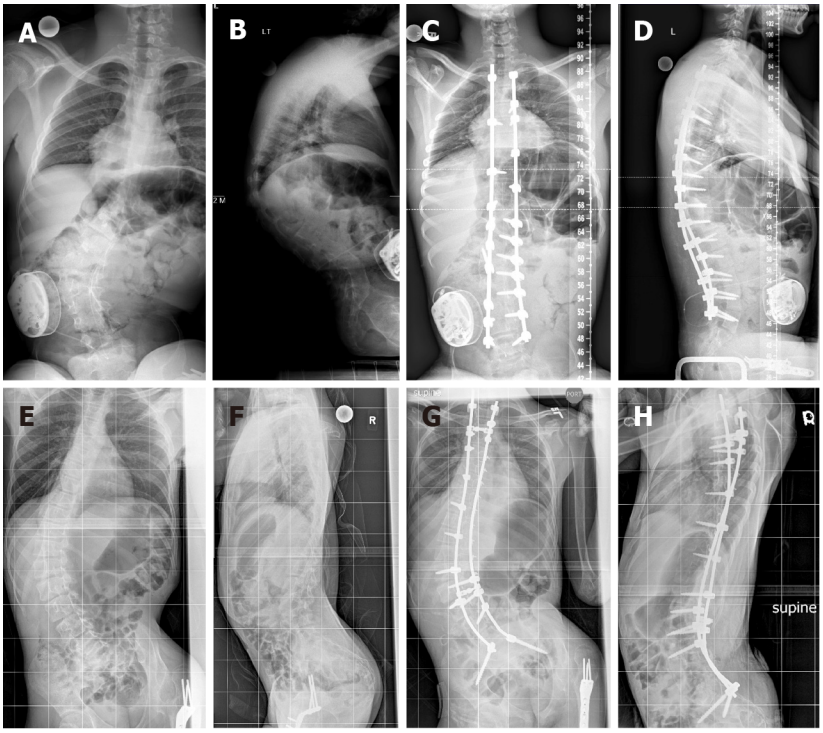

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Figure 1 Sample cases of patients who were fused short of the pelvis or whose fusion included the pelvis. A, B: Preoperative anteroposterior (A) and lateral (B) radiographs demonstrating scoliosis with a lumbar curve Cobb angle of 58° and pelvic obliquity of 12°; C, D: Fusion was stopped at L5, and postoperative anteroposterior (C) and lateral (D) radiographs show the lumbar curve Cobb angle at 8° and pelvic obliquity at 3°; E, F: Preoperative anteroposterior (E) and lateral (F) radiographs demonstrating scoliosis with a lumbar curve Cobb angle of 52° and pelvic obliquity of 19°; G, H: Fusion was carried out to the pelvis, and postoperative anteroposterior (G) and lateral (H) radiographs show a lumbar curve Cobb angle of 48° and pelvic obliquity of 12°.

selection bias. This might limit the generalizability of the present study, but the conclusion that in a select patient population, posterior fusion does not necessarily have to include the pelvis remains valid. In addition, our outcomes focused on complications. Other factors that can affect surgical planning, like patient and caregiver satisfaction, were not assessed. Additional studies that focus on patient reported outcomes in this patient population will provide valuable insights.

CONCLUSION

In conclusion, this study demonstrated that in children with CP scoliosis, fusion short of the pelvis can lead to acceptable final pelvic tilt in some cases and may decrease the risk of developing post-operative complications.

ARTICLE HIGHLIGHTS

Research background

The distal extent of the fusion in children with cerebral palsy scoliosis is a controversial topic. There is not enough evidence on whether it is necessary to include the pelvis in the distal fusion to correct for pelvic obliquity in these patients.

Research motivation

This study was carried out to fill the gap in the literature on whether it is necessary to fuse to the pelvis when correcting cerebral palsy scoliosis. The need for a homogeneous cohort (*i.e.* children with cerebral palsy and not other forms of neuromuscular scoliosis) was an additional reason for carrying out the study.

Research objectives

The primary objective was to compare the radiographic outcome (Cobb angles and pelvic obliquity) of cerebral palsy scoliosis treatment in children who were fused to the pelvis *vs* those who were fused to

L4/L5. The secondary objective was to determine the complications associated with each of the two procedures.

Research methods

The study was a retrospective, cohort study that utilized chart and radiographic review to determine the outcomes and complications associated with cerebral palsy scoliosis correction in children who were fused to L4/L5 as compared to those fused to the pelvis.

Research results

In the analysis of 47 patients, the L5 tilt was corrected by 60% in patients fused to the pelvis, comparable to the 67% achieved in patients fused to L4/L5 (P = 0.22). The pelvic obliquity was also corrected by a similar degree; 43% in patients fused to the pelvis and 36% in patients fused to L4/L5 (P = 0.12). As for complications, patients fused to the pelvis had a higher number of total complications (63.0% *vs* 30%, respectively, P = 0.025).

Research conclusions

Fusing to the pelvis in cerebral palsy scoliosis did not achieve better correction of patients' pelvic obliquity and L5 tilt. However, it did increase the risk of postoperative complications. Therefore, spinal fusion can be stopped at the distal lumbar levels in a select patient population, without necessarily compromising the surgical outcomes.

Research perspectives

Future studies can investigate delineating specifically which patients might benefit from including the pelvis in their distal fusion. This might aid the surgeons in their preoperative planning and in guiding their choice of surgical technique.

FOOTNOTES

Author contributions: Jardaly AH, Conklin MJ, and Gilbert SR designed the research study; Strom SF, Hess MC, Jardaly AH, Conklin MJ, and Gilbert SR performed the data collection; Jardaly AH analyzed the data; Strom SS, Hess MC, and Jardaly AH wrote the manuscript; all authors thoroughly edited the manuscript; all authors have read and approve the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Comparing complications of outpatient management of slipped capital femoral epiphysis and Blount's disease: A database study

Achraf Jardaly, Timothy W Torrez, Gerald McGwin, Shawn R Gilbert

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Abstract

BACKGROUND

Currents trends in pediatric orthopaedics has seen an increase in surgeries being successfully completed in an outpatient setting. Two recent examples include slipped capital femoral epiphysis (SCFE) and Blount's disease. Surgical indications are well-studied for each pathology, but to our knowledge, there is an absence in literature analyzing safety and efficacy of inpatient *vs* outpatient management of either condition. We believed there would be no increase in adverse outcomes associated with outpatient treatment of either conditions.

AIM

To investigate whether outpatient surgery for SCFE and Blount's disease is associated with increased risk of adverse outcomes.

METHODS

The 2015-2017 American College of Surgeons National Surgical Quality Improvement Program Pediatric Registries were used to compare patient characteristics, rates of complications, and readmissions between outpatient and inpatient surgery for SCFE and Blount's disease.

RESULTS

Total 1788 SCFE database entries were included, 30% were performed in an

outpatient setting. *In situ* pinning was used in 98.5% of outpatient surgeries and 87.8% of inpatient surgeries ($P < 0.0001$). Inpatients had a greater percent of total complications than outpatients 2.57% and 1.65% respectively. Regarding Blount's disease, outpatient surgeries constituted 41.2% of the 189 procedures included in our study. The majority of inpatients were treated with a tibial osteotomy, while the majority of outpatients had a physeal arrest ($P < 0.0001$). Complications were encountered in 7.4% of patients, with superficial surgical site infections and wound dehiscence being the most common. 1.6% of patients had a readmission. No differences in complication and readmission risks were found between inpatients and outpatients.

CONCLUSION

The current trend is shifting towards earlier discharges and performing procedures in an outpatient setting. This can be safely performed for a large portion of children with SCFE and Blount's disease without increasing the risk of complications or readmissions. Osteotomies are more commonly performed in an inpatient setting where monitoring is available.

Key Words: Outpatient surgery; Early discharge; Slipped capital femoral epiphysis; Blount's disease

Core Tip: In our retrospective analysis of common complications of both slipped capital femoral epiphysis and Blount's disease using National Surgical Quality Improvement Program database. We showed equivocally that treating both these conditions as an outpatient was safe and effective.

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INTRODUCTION

In recent years, an increasing number of orthopaedic surgeries have been performed in an outpatient setting[1]. A study examining pediatric fracture trends demonstrated a threefold increase in the use of outpatient services for the surgical fixation of fractures from 1996 to 2006[2]. Though outpatient surgery provides a lower initial cost, several factors like patient safety, complications, and readmissions need to be considered[3].

Obesity in children has reached epidemic proportions. According to the Centers of Disease Control and Prevention, 1 out of 5 individuals less than 19 years of age are obese[4]. As such, it is anticipated that adverse health outcomes related to obesity will increase. From an orthopaedic perspective, childhood obesity is considered to be a significant risk factor for both slipped capital femoral epiphysis (SCFE) and Blount's disease[5,6]. A better understanding of both diseases and their respective treatment options would benefit children and their families.

Despite the surgical options for SCFE and Blount's disease being well-studied, to our knowledge, there is no literature comparing inpatient *vs* outpatient management of either condition[6,7]. Therefore, we sought to use a large pediatric database to compare the complication and readmission rates between treatment in the inpatient and outpatient setting. Our hypothesis was that there would be no increased risk of adverse outcomes associated with the outpatient treatment of both conditions.

MATERIALS AND METHODS

The American College of Surgeons National Surgical Quality Improvement Program (NSQIP) Pediatric Registry was queried for the years 2015, 2016, and 2017[8]. As information in this database is de-identified and HIPAA compliant, institutional review board approval is not required.

NSQIP prospectively collects data on patient demographics, risk factors, and operative details. The database follows patients for 30 d after surgeries to document discharge status, complications, readmission, and reoperation. The 2017 NSQIP Pediatric database includes 113922 cases from 109 hospitals. Cases with codes corresponding for the International Classification of Diseases, ninth and tenth revisions (ICD-9 and ICD-10) primary diagnosis of SCFE or Blount's disease were selected. Procedures were defined as outpatient if patients were discharged on the day of the surgery.

For SCFE, patients from 9 to 16 years were included. Treatment options were divided into *in situ* pinning and open treatment. Open treatment includes osteotomy, open reduction, and internal fixation. For pediatric Blount's disease, patients older than 10 years were excluded. Treatment was categorized as external fixation, osteotomy, or physeal arrest. Osteotomy includes proximal tibial osteotomy with or without fibular osteotomy or excision. Physeal arrest includes epiphysiodesis and hemiepiphysiodesis with any method (*e.g.* guided growth). Patients were excluded if their primary surgery was not congruent with their primary diagnosis (*e.g.* distal femur lengthening for SCFE, or tumor/cyst excision for Blount's disease).

In addition to the common complications documented in the database, we considered a discharge to an acute care setting or facility which was not home as a complication. If a case had multiple related complications, then it was recorded as one complication. For example, a patient with both superficial wound dehiscence and superficial surgical site infection (SSI) was counted as one complication under superficial SSI. No patient had multiple unrelated complications. We included both reoperations and readmissions not requiring an operation in "readmissions.".

Statistical analysis was carried out using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA). ANOVA, Wilcoxon signed rank-test, Fisher's exact tests, and χ^2 tests were used to compare variables between the outpatient and the inpatient settings. Odds ratios (OR) with 95%CI were calculated when differences in adverse outcomes were exhibited between the inpatient and outpatient settings. P values < 0.05 were considered to be statistically significant.

RESULTS

SCFE

Out of 1797 procedures for SCFE, 46% were performed as an outpatient. 93.6% of children admitted postoperatively were discharged within 3 days, with 47.7% being discharged on postop day (POD) 1 and 39.4% on POD 2. Patients in both settings were similar with respect to age. Small differences existed regarding the weight, sex, and race of patients. There were more males and white patients receiving outpatient surgeries in comparison to the inpatient setting noting more female and black patients. Outpatients had a higher percentage of American Society of Anesthesiologists Classification (ASA) classes 1 and 2 and a lower percentage of ASA class 3 compared to inpatients. Patient details can be found in Table 1. *In situ* pinning was the most common procedure, constituting 98.5% of outpatient surgeries and 87.8% of inpatient surgeries (P < 0.0001).

Total 1.6% of outpatients and 1.2% of inpatients had complications (P = 0.50), and the readmissions rates were 1.1% and 1.44%, respectively (P = 0.89). The nature of complications and causes of readmission are found in Table 2. There was no statistically significant difference in individual adverse outcomes except for bleeding. Bleeding was the most common complication among inpatients and did not occur in outpatients. None of these patients had a preoperative bleeding disorder. 12 of the 15 cases of bleeding requiring transfusion occurred with open procedures (Osteotomy and internal fixation) while 3 occurred during in situ pinning (P < 0.0083). The overall risks of SCFE recurrence and femoral neck fractures for outpatient and inpatient was 0.55% and 0.64% respectively. Three inpatients initially discharged on POD 1 required readmission for postop pain management.

There were 3.5x the total number of complications in the inpatient SCFE group but the mean number of complications between the two groups was not significant (P = 0.292). There were 3.3x the number patients that developed complications but OR was not statistically significant (OR = 0.66, 95%CI: 0.31-1.41). Similarly, no difference was found regarding odds of readmission (OR = 1.12, 95%CI: 0.20–6.16).

Blount's disease

Total 189 procedures for Blount's disease were included. 41.2% were performed in an outpatient setting. 54.1% of admitted patients were discharged on POD 1, and 30.6% were discharged on POD 2. Patients in both settings had similar sex, race, BMI, and ASA distributions, but statistically significant differences were found in their age. Outpatients were younger by (0.7 year) (Table 1). There were also differences in the procedures used in both settings (P < 0.0001). Osteotomy was the most common procedure among inpatients (64%), whereas it was not performed in an outpatient setting. 98.7% of outpatients were treated with physeal arrest, as compared to 34.2% of inpatients.1.3% of inpatients and 1.8% of outpatients were treated with external fixation.

7.4% of patients experienced complications (Table 3). Superficial SSI and wound dehiscence were the most frequent complications. Individual and total risk of complications and readmissions were not different between both settings (P > 0.05) so no ORs were calculated.

DISCUSSION

There is a shifting trend towards performing procedures in an outpatient setting[9]. In the current study

Table 1 Patient demographics, *n* (%)

	SCFE		Blount's disease	
	Outpatient (*n* = 553)	Inpatient (*n* = 1244)	Outpatient (*n* = 78)	Inpatient (*n* = 111)
Age (yr), mean ± SD	12.6 ± 1.4	12.5 ± 1.6	6.0 ± 2.8[a]	6.7 ± 2.0[a]
Sex				
Female	181 (32.73)[a]	490 (39.39)[a]	52 (66.7)	70 (63.1)
Male	372 (67.27)[a]	754 (60.61)[a]	26 (33.3)	41 (36.9)
Weight (kg), mean ± SD	71.5 ± 18.2	73.3 ± 20.3	38.6 ± 23.5[a]	48.6 ± 27.1[a]
Missing	2	3	0	0
Race				
White	248 (44.85)[a]	429 (34.49)[a]	17 (21.8)	20 (18.0)
Black	153 (27.67)[a]	441 (35.45)[a]	46 (60.2)	63 (56.8)
Hispanic	74 (13.38)[a]	158 (12.7)[a]	6 (7.7)	13 (11.7)
Other minorities	33 (5.6)[a]	41 (3.29)[a]	3 (3.8)	5 (4.5)
Unknown/Not reported	47(8.5)[a]	175 (14.07)[a]	6 (7.7)	10 (9.0)
ASA				
1	182 (32.91)	399 (32.07)	24 (30.8)	21 (18.9)
2	340 (61.48)	725 (58.28)	42 (53.8)	61 (55.0)
3	29 (5.24)	116 (9.32)	12 (15.4)	27 (24.3)
4	1 (0.18)	1 (0.08)	0	2 (1.8)
None assigned	1 (0.18)	3 (0.24)	0	0

[a]$P < 0.05$ between groups.

ASA: American Society of Anesthesiologists Classification; SCFE: Slipped capital femoral epiphysis.

based on results from the NSQIP Pediatric database, 46% of SCFE procedures and 41% of Blount's procedures were performed as outpatients.

Several studies report a decline in the incidence of SCFE[10-12]. As obesity rates have been increasing, it is unusual for fewer children to suffer from SCFE. One thing to consider is the methodology of the studies, which rely on databases. Most large registries report inpatient admissions. Same-day surgeries and procedures performed in ambulatory surgery centers are more difficult to capture, but the shift towards outpatient surgery could contribute to the apparent decrease in the incidence of SCFE. In 2000, outpatient SCFE procedures represented 23% of operatively treated SCFEs[13]. This percentage more than doubled according to our results. In addition, NSQIP does not include data from ambulatory centers, so outpatient procedures might constitute more than half of all SCFE surgical correction. Future studies investigating the true incidence of SCFE with outpatient adjustment would provide valuable information.

Performing procedures in an outpatient setting has several advantages. One significant benefit is the lower patient and hospital cost associated with early patient discharge[14]. In addition, several studies showed that patient satisfaction is inversely correlated with the length of hospital stay[15]. A study comparing inpatients and outpatients satisfaction following hip and knee arthroplasty demonstrated that satisfaction was high in both groups, but in areas of differences, outpatients had higher scores[16]. For children, this effect might be more pronounced, and performing outpatient surgeries can benefit their psychological well-being[17]. However, outpatient surgeries can have higher rates of adverse outcomes in some contexts, particularly with SSI[18]. Arshi *et al*[19] found that outpatient total knee arthroplasties had a higher chance of revision compared with inpatient care. Therefore, comparative studies for specific conditions are needed in this area.

Though an outpatient setting is an attractive option for patients and physicians, postoperative pain needs be considered[17]. Previous studies showed that children discharged home at the day of surgery had higher pain score than inpatients[20]. Even in admitted patients, Mather and Mackie reported that 17% of children had severe pain on POD 1[21]. In the present analysis, only 3 SCFE patients (0.24%) required readmission for pain. These patients were initially discharged on POD 1. None of the SCFE outpatients or any patients treated for Blount's disease had pain requiring readmission. Therefore, it is possible for the vast majority of surgical patients to benefit from early discharge without the need for

Table 2 Adverse outcomes in slipped capital femoral epiphysis patients, *n* (%)

	Outpatient (*n* = 544)	Inpatient (*n* = 1244)
Complication		
Non-routine discharge	6 (1.1)	5 (0.40)
Superficial SSI	1 (0.18)	5 (0.40)
Superficial wound dehiscence	1 (0.18)	6 (0.48)
Postop *C. diff* infection	1 (0.18)	0
Bleeding requiring transfusion	0[a]	15 (1.21)[a]
Venous thrombosis	0	1 (0.08)
Total number of patients with complications	9 (1.65)	30 (2.41)
Total number of complications	9 (1.65)	32 (2.57)
Reoperation		
SCFE	0	7 (0.56)
Hip infection	0	1 (0.08)
Femoral neck fracture	3 (0.55)	1 (0.08)
Closed reduction of hip dislocation	1 (0.18)	0
Fracture of hip/pelvis	0	1 (0.08)
Not documented	0	2 (0.20)
Total complication	4 (0.73)	12 (0.96)
Readmission without operation		
Superficial SSI	0	1 (0.08)
Pain	0	3 (0.24)
Not documented	2 (0.24)	4 (0.32)
Total readmission	6	18

[a]$P < 0.05$ between groups.
SCFE: Slipped capital femoral epiphysis; SSI: Surgical site infection.

inpatient management of pain. Techniques for anesthesia have improved significantly, and adequate postoperative analgesia can be achieved by giving caregivers ample pediatric-specific instructions and using multimodal medications[20].

Disease-specific and surgery-specific considerations also need to be investigated. One such consideration is the early return to weight-bearing which could increase the risk of femoral neck fractures in patients with SCFE[22]. Femur fractures in our SCFE population were rare and did not differ significantly based on the treatment setting. Nonetheless, for unstable slips where physician judgment deems strict non-weight-bearing to be necessary, patients might benefit from hospital admission (with inpatient physical therapy) to help enforce weight-bearing restrictions when compliance is an issue. The most common complications of SCFE include osteonecrosis, chondrolysis, fixation failure, and slip progression[23]. Osteonecrosis and chondrolysis are largely related to the nature of the slips rather than the surgical approach[23]. 0.56% of patients required a reoperation for SCFE, indicating fixation failure and/or slip progression. This rate was not different based on the setting of the surgery. Other common complications like SSI and wound dehiscence were also similar between the groups. The only individual complication that was different between both groups was bleeding requiring a transfusion. However, this was confounded with open procedures. Open procedures are more invasive, and bleeding is a well-known complication[7]. Such procedures are reserved for severe slips requiring more complex procedures, and it is recommended that they be admitted for inpatient monitoring. After adjusting the analysis for the type of surgery, the inpatient and outpatient settings did not have different odds ratio of complications or readmissions.

Surgery for Blount's disease, though technically difficult, is not commonly associated with major complications other than recurrence[24]. Infections, nerve injuries, and compartment syndromes can still occur[25]. 7.4% of Blount's patients had a complication in this study, most commonly superficial SSI and wound dehiscence. Patients selected to be treated in an outpatient setting can benefit from

Table 3 Adverse outcomes in Blount's patients, *n* (%)

Adverse outcome	Outpatient (*n* = 78)	Inpatient (*n* = 111)
Complication		
Non-routine discharge	1 (1.3)	0
Superficial SSI	1 (1.3)	5 (4.5)
Superficial wound dehiscence	4 (5.1)	2 (1.8)
Sepsis	1 (1.3)	0
Total complications	7 (9.0)	7 (6.3)
Readmission without operation		
Not documented	0	1 (0.9)
Reoperation		
Incision and drainage	1 (1.3)	0
Neuroplasty (common peroneal nerve)	0	1 (0.9)
Total readmissions	1 (1.3)	2 (1.8)

No *P* values < 0.05. SSI: Surgical site infection.

education about meticulous wound care and early signs of infection, and our results showed that rates of infections and overall complications were not different between both settings. This confirms our hypothesis that outpatient procedures are not associated with increased morbidity.

Careful patient selection is still needed to limit complications and readmissions. Patients with ASA 1 or 2 are considered suitable for outpatient surgery[17]. 90.3% of all the patients included in this study meet this requirement. Those with ASA 3 can still receive outpatient surgery, but they might have an increased risk of admission[17]. In addition, attention should be given to comorbidities and prior surgical or anesthetic complications. Nonetheless, a large portion of children with SCFE and Blount's disease can benefit from outpatient surgery.

To capture a large number of procedures, we used the NSQIP Pediatric Database. This is not without limitations. Data collected was from numerous hospitals, so there could be differences in the surgical techniques, indications for surgery, and selection criteria for inpatient *vs* outpatient procedures. Also, all cases included are surgeries performed in a hospital setting. Cases from ambulatory surgery centers are not part of the database. This means that even more procedures are performed in the outpatient setting. However, numerous studies have shown that ambulatory centers have similar outcomes to hospital outpatients, so the conclusion that outpatient surgery does not increase the risk of complications is not undermined[25,26]. In addition, patients were followed for 30 d. Long term complications like growth arrest and femoroacetabular impingement for SCFE and recurrence of Blount's disease may differ. Symptoms before and after surgery are not available. Despite these limitations, this study provides a representative sample of surgically managed cases of SCFE and Blount's disease and is the first to investigate short-term readmission and complication rates between of these outpatient procedures. Additionally, the prospective data collection and a priori definitions of complications improve the quality of data regarding complications compared to retrospective data collection or databases utilizing only coded complications.

CONCLUSION

In conclusion, our results indicate that performing outpatient surgeries for SCFE and Blount's disease is a viable option. Careful selection criteria need to be applied, but a large number of children can be surgically-treated as outpatients which does not affect the odds for early postoperative complications or readmissions.

ARTICLE HIGHLIGHTS

Research background

Currents trends in pediatric orthopaedics has seen an increase in surgeries being successfully completed

in an outpatient setting.

Research motivation
Limited data is available on safety and efficacy of managing slipped capital femoral epipphysis and Blount's disease in the outpatient setting.

Research objectives
Is outpatient management safe and effective for slipped capital femoral epipphysis and Blount's disease in the outpatient setting.

Research methods
Retrospective analysis of a large multi-institutional database.

Research results
In summary complications were minimal in outpatient surgical management for slipped capital femoral epiphysis and Blount's disease in the outpatient setting.

Research conclusions
Surgeons should consider outpatient management for both slipped capital femoral epiphysis and Blount's disease.

Research perspectives
This study should prompt future research in outcomes of outpatient management of other previous inpatient pediatric orthopaedic procedures.

FOOTNOTES

Author contributions: Jardaly A contributed to the manuscript preparation, data collection, revisions; Torrez TW contributed to the manuscript preparation, data collection, revisions; McGwin G contributed to the data analysis and statistics; Gilbert SR contributed to the manuscript preparation and was the principal investigator.

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ORIGINAL ARTICLE

Retrospective Study

Minimally invasive outpatient management of iliopsoas muscle abscess in complicated spondylodiscitis

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Abstract

BACKGROUND

Iliopsoas muscle abscess (IPA) and spondylodiscitis are two clinical conditions often related to atypical presentation and challenging management. They are both frequently related to underlying conditions, such as immunosuppression, and in many cases they are combined. IPA can be primary due to the hematogenous spread of a microorganism to the muscle or secondary from a direct expansion of an inflammatory process, including spondylodiscitis. Computed tomography-guided percutaneous drainage has been established in the current management of this condition.

AIM

To present a retrospective analysis of a series of 8 immunocompromised patients suffering from spondylodiscitis complicated with IPA and treated with percutaneous computed tomography-guided drainage and drain insertion in an outpatient setting.

METHODS

Patient demographics, clinical presentation, underlying conditions, isolated microorganisms, antibiotic regimes used, abscess size, days until the withdrawal of the catheter, and final treatment outcomes were recorded and analyzed.

RESULTS

All patients presented with night back pain and local stiffness with no fever. The laboratory tests revealed elevated inflammatory markers. Radiological findings of

spondylodiscitis with unilateral or bilateral IPA were present in all cases. *Staphylococcus aureus* was isolated in 3 patients and *Mycobacterium tuberculosis* in 2 patients. Negative cultures were found in the remaining 3 patients. The treatment protocol included percutaneous computed tomography-guided abscess drainage and drain insertion along with a course of targeted or empiric antibiotic therapy. All procedures were done in an outpatient setting with no need for patient hospitalization.

CONCLUSION
The minimally invasive outpatient management of IPA is a safe and effective approach with a high success rate and low morbidity.

Key Words: Iliopsoas abscess; Spondylodiscitis; Percutaneous drainage; Minimally invasive; Outpatient; Immunocompromised

Core Tip: Eight patients diagnosed with spondylodiscitis complicated with iliopsoas muscle abscess were managed with minimally invasive percutaneous computed tomography-guided drainage, placement of a drain, and proper antibiotic treatment in an outpatient setting. Complete recession of the symptoms with no recurrence after 6 mo was observed. The minimally invasive outpatient management of iliopsoas muscle abscess is a safe and effective approach with a high success rate and low morbidity.

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INTRODUCTION

Iliopsoas muscle abscess (IPA) is a rare infective clinical condition often related to nonspecific symptoms and a variety of etiologies[1]. It was first described by Mynter in 1881 and was characterized as "acute psoitis"[2]. Two proposed mechanisms lead to IPA. Primary IPAs are caused by a hematogenous spread of an infective microorganism that leads to IPA formation due to the muscle's rich vascularity, especially in immunocompromised patients. Secondary IPAs are developed by a contiguous spread of an intra-abdominal inflammatory process or by musculoskeletal conditions such as spondylodiscitis, sacroiliitis, or tuberculosis of the spine[1,3,4].

Spondylodiscitis is the most common form of spinal infection, affecting the intervertebral disc and the adjacent vertebral bodies and can present isolated or combined with other underlying conditions such as infections, malignancy, and immunosuppression[5]. Pyogenic spondylodiscitis can result in IPA due to direct expansion into the iliopsoas.

Symptoms of IPA may be insidious and nonspecific due to the location of the iliopsoas muscle, but the classical clinical presentation described in the literature includes the triad of fever, back pain, and limp[6,7]. Due to the atypical clinical features, diagnosis is oftentimes delayed leading to increased morbidity and mortality. Once an IPA is suspected, computed tomography (CT) scan is recommended, with a high sensitivity rate approaching 100%, whereas magnetic resonance imaging (MRI) of the spine is the most indicative imaging for spondylodiscitis[4,8]. There is no uniform treatment strategy for IPA. Traditionally, surgical drainage of the abscess along with a broad-spectrum antibiotic treatment was the preferred treatment[1,9,10]. However, more recent literature reports that the percutaneous CT-guided abscess drainage is a safe and equally effective alternative[1,8,11]. The purpose of the current study was to present and evaluate a case series of 8 patients diagnosed with spondylodiscitis complicated with IPA. The patients were managed with antimicrobial therapy, minimally invasive percutaneous CT-guided drainage, and the addition of a short-term drain insertion in an outpatient setting.

MATERIALS AND METHODS

A retrospective collection and analysis of all radiologically diagnosed cases of IPA that were treated with CT-guided percutaneous drainage from 2016 to 2020 in the department of Interventional Radiology of a tertiary University hospital was performed. All cases initially presented to the spinal outpatient

clinic complaining of back pain and were diagnosed with spondylodiscitis and IPA formation after an MRI and a CT scan. Records were extracted from the Interventional Radiology department's database. Data were reviewed for patient demographics, underlying conditions, isolated microorganisms, antibiotic regimes used, abscess size, days until the withdrawal of the catheter, and final outcome.

All abscesses were defined as secondary IPAs due to the concurrent presence of spondylodiscitis. Two patients were diagnosed specifically with tuberculosis of the spine. There was no neurological compromise, spinal instability, or bone deformity present due to spondylodiscitis.

Treatment success was marked by clinical and laboratory improvement along with radiological confirmation of recession of the abscess and eventually catheter removal. All patients were clinically evaluated 6 mo after the end of their treatment.

CT-guided percutaneous drainage

All draining procedures were performed by direct insertion of a 12 Fr pigtail catheter into the abscess cavity. Before the procedure, a CT and MRI scan were performed. Values of international normalized ratio less than 1.5 and platelet count greater than 50000/μL were required to proceed with the drainage, and antiplatelet or anticoagulation medication had to be discontinued accordingly. Patients were placed in the prone position in most cases (7 out of 8 patients). The placement decision was made depending on the best approach to the abscess cavity. All procedures were performed under local anesthesia and aseptic conditions. After an initial CT scan for approach planning, the trocar pigtail catheter was advanced into the abscess cavity under CT guidance. When the trocar reached the middle of the fluid collection it was withdrawn while the catheter was advanced and secured in position (Figure 1). Manual aspiration of the fluid was then performed, and the catheter was connected to a drainage bag. The inserted drain was removed if there was no drainage for 48 h.

RESULTS

A total of 8 patients that underwent CT-guided percutaneous IPA drainage were included in the study (Table 1). Their mean age was 52.6 ± 20.8-years-old, and there were six unilateral and two bilateral cases, a total of 10 abscesses. All cases were secondary; six were in immunocompromised patients [renal failure, HIV, intravenous (IV) drugs] with spondylodiscitis and two were in patients diagnosed with tuberculosis of the spine.

All patients presented at the spine outpatient clinic complaining of back pain for at least 3 mo with worsening at night, and 1 patient also mentioned weight loss. At clinical examination, there was local sensitivity and palpable muscle spasm found in all patients with no neurological compromise. All patients remained afebrile. From the laboratory investigation, there was an increase in inflammatory markers (C-reactive protein and erythrocyte sedimentation rate).

The diagnosis was confirmed by MRI followed by CT. According to imaging calculations, the mean abscess size was 6.3 ± 2.1 cm. There was no bone deformity or spinal degeneration observed. The drainage procedure was arranged immediately and performed in the next 1-3 d from the initial diagnosis. A 12 Fr pigtail drain was inserted in all cases, as previously described. The average time until the withdrawal of the catheter was 10 ± 2 d.

Microbiology samples from the abscess fluid were sent in all cases. *Staphylococcus aureus* was isolated in 3 cases, *Mycobacterium tuberculosis* was isolated in 2 patients, and there was no specific microorganism isolated in 2 renal impairment/dialysis patients and 1 IV drug user. All patients initially received empiric antibiotic therapy with ciprofloxacin and clindamycin orally. After the culture results, patients with *Staphylococcus aureus* culture isolation received a targeted 2-wk course of intravenous vancomycin and oral rifampicin with daily outpatient visits, followed by oral linezolid and rifampicin for another 6 wk. The tuberculosis patients underwent a 9-mo antimicrobial treatment with oral isoniazid, ethambutol, and rifampicin, whereas the patients with no specific microorganism isolated received an 8-wk empiric antibiotic treatment as presented in Table 2. All abscesses were successfully drained on the first attempt, and all patients had a complete resolution of symptoms. There were no recurrences at the 6-mo follow-up.

DISCUSSION

We present a case series of 8 patients suffering from spondylodiscitis complicated with IPA, successfully treated with a minimally invasive approach of combined percutaneous abscess drainage with drain insertion and antibiotic therapy. Immunosuppression is the predominant underlying condition in IPA and may be responsible for the insidious presenting signs and symptoms[9]. In the current series, there was a higher prevalence of IPA in patients that were on renal dialysis, immunocompromised by HIV, or IV drug users. Moreover, tuberculosis is linked to secondary IPA due to vertebral involvement[11-13]. Although tuberculosis is rare, there were 2 cases of secondary IPA in patients with tuberculosis of the

Table 1 Patient's demographics

Patient	Sex	Age in yr	Underlying condition	Site	Position	Size in cm	Procedure time in min	Presenting complaint	Catheter withdrawal in d	Microbiologic cultures
1	Male	76	Renal failure-dialysis	Unilateral	Prone	4.5	15	Back pain	8	Negative
2	Female	69	Renal failure-dialysis	Unilateral	Prone	6.4	15	Back pain, weight loss	10	Negative
3	Male	74	Renal failure-dialysis	Bilateral	Prone	7.5/4.5	25	Back pain	8	*Staphylococcus aureus*
4	Female	68	Renal failure-dialysis	Unilateral	Prone	4.4	10	Back pain	9	*Staphylococcus aureus*
5	Female	34	HIV	Bilateral	Prone	5.5/4.3	25	Back pain	8	*Staphylococcus aureus*
6	Male	35	IV drug user	Unilateral	Supine	8.3	10	Back pain	13	Negative
7	Male	38	Tuberculosis	Unilateral	Prone	7.5	15	Back pain	11	*Mycobacterium tuberculosis*
8	Female	27	Tuberculosis	Unilateral	Prone	10.4	15	Back pain	14	*Mycobacterium tuberculosis*

IV: Intravenous.

Table 2 Culture results and antibiotic treatment

Microorganism	*n*	Antibiotic treatment	Duration
Staphylococcus aureus	3	Rifampicin PO - Vancomycin IV	2 wk
		Rifampicin PO - Linezolid PO	6 wk
Mycobacterium tuberculosis	2	Rifampicin PO - Isoniazid PO - Ethambutol PO	9 mo
Negative cultures, renal impairment patients	2	Vancomycin IV - Ciprofloxacin PO	8 wk
Negative cultures, IV drug user	1	Ciprofloxacin PO - Clindamycin PO	4 wk
		Ciprofloxacin PO - Rifampicin PO	3 wk

IV: Intravenous; PO: By mouth (*per* os).

spine.

The clinical triad of IPA symptoms as described by Mynter[2] in 1881 includes back pain, limping, and fever. Subsequent studies have identified more nonspecific symptoms such as weight loss, lower extremity pain, lower extremity edema, gastrointestinal symptoms, and a palpable mass[8]. The laboratory findings include elevated white blood cell count, C-reactive protein, and erythrocyte sedimentation rate as well as anemia[3,4]. In the present case series, none of the patients presented with the typical IPA symptomatology. The patients' underlying conditions along with the raised inflammatory markers guided the physicians to suspect an inflammatory condition of the spine.

The final diagnosis of IPA is confirmed by the imaging findings. Several studies recommend ultrasound as the initial radiological investigation. However, it is an operator-dependent procedure with a low diagnostic rate[1,9,14]. CT scan is considered to be the "gold standard" for a definitive diagnosis of IPA, and MRI adds more detailed imaging of the abscess wall, the soft tissues, and the surrounding structures without the need for IV contrast infusion[3,15-17]. Both MRI and CT scans were performed in the current study and revealed signs of spondylodiscitis with unilateral or bilateral IPA formation in all patients. Although IPA is mainly described as an outcome of spondylodiscitis[7], literature also describes spondylodiscitis as a complication of an established IPA[18]. Therefore, it could not be clearly stated which condition was presented first. Spondylodiscitis, however, did not require invasive treatment in contrast to the IPA formation.

The literature traditionally suggests early surgical management of the IPA, which suggests a long in-hospital stay. The surgical procedure of choice, according to Ricci *et al*[9] in 1986, was abscess drainage through a lower abdominal muscle-splitting, extraperitoneal incision. In more recent years, with the evolution of interventional radiology, minimally invasive percutaneous drainage of retroperitoneal abscesses, including IPA, is the treatment method of choice[11]. This approach is preferred especially for

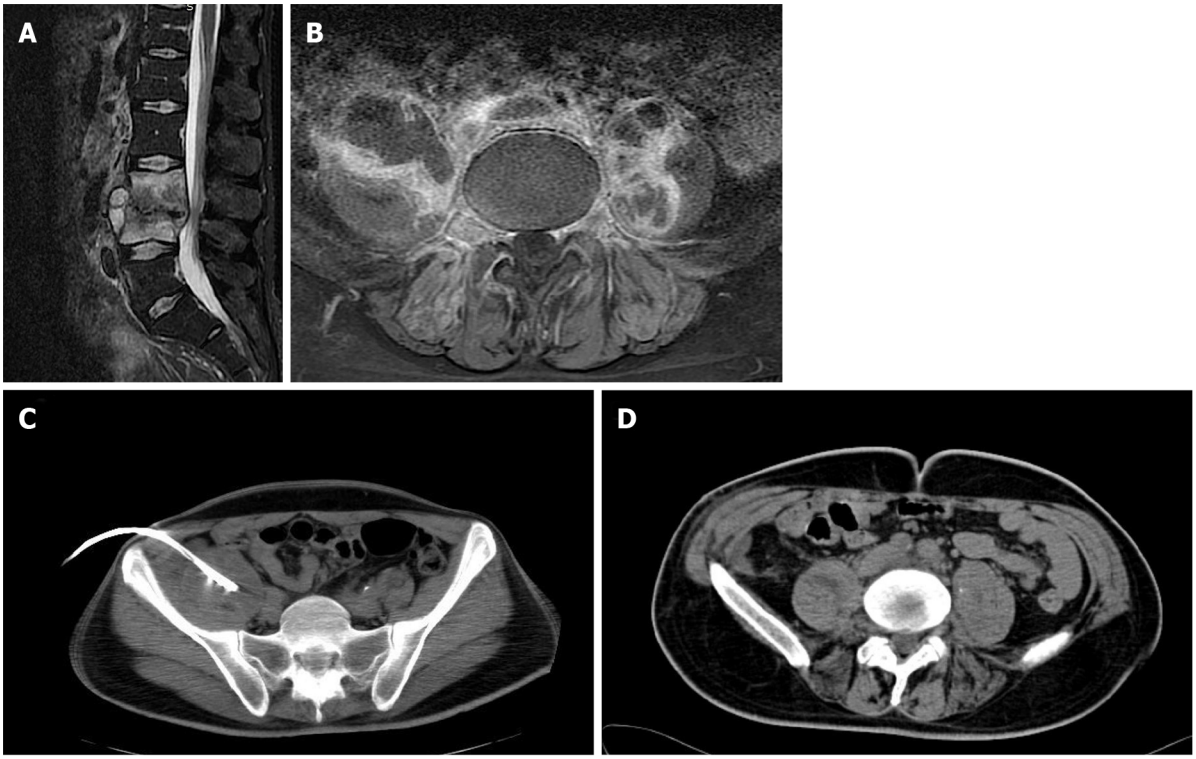

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Figure 1 A 35-year-old patient with a history of intravenous drug use presenting with severe low back pain. A: T2 weighted image sagittal image reveals a high-intensity signal of the L3-L4 vertebrae, disk involvement, and paravertebral fluid collections; B: T1 weighted image axial image with contrast enhancement reveals bilateral iliopsoas abscesses; C: The corresponding computed tomography image with the pigtail catheter inserted in the right iliopsoas abscess; D: The computed tomography image after the catheter removal revealed complete resolution of the abscess.

immunocompromised patients, as it eliminates the need for general anesthesia and is also associated with a shorter hospital stay, minimizing morbidity and mortality. There is currently no literature describing the management of such patients with a drain insertion in an outpatient setting. In the current series, all patients were managed as outpatients. All patients underwent CT-guided drainage and drain insertion without delay from the time of diagnosis. The drain insertion increased the success rate of the drainage, and no repeat procedures were necessary.

Empiric antibiotic therapy should cover against *Staphylococcus aureus* and gram-negative and gram-positive microorganisms, including bowel flora and common urinary tract infection bacteria, and targeted therapy should be commenced immediately after the culture results[14]. For mycobacterial infections, a 9-mo conventional antituberculosis therapy was applied. For non-mycobacterial infections, as all cases presented with vertebral involvement, the minimum duration of the antibiotic treatment was 8 wk, including at least 2 wk of IV vancomycin, and prolonged according to laboratory and radiological findings. Those receiving IV vancomycin visited the outpatient clinic daily for the first 2 wk for the infusions.

The drain catheter remained in place until no drainage was observed for 2 consecutive days. A follow-up CT scan was performed between days 7 and 14 to confirm abscess recession.

The current study has several limitations. First, it is a single-center study of a small pilot patient group, which reflects the rarity of the condition. Second, no control group was recruited. Moreover, the retrospective study design might introduce recall or patient selection bias.

CONCLUSION

The minimally invasive outpatient management of IPA is a safe and effective approach with a high success rate and low morbidity.

ARTICLE HIGHLIGHTS

Research background

There has been an evolution in the management of complicated spondylodiscitis with iliopsoas muscle abscess (IPA) formation through the years and computed tomography (CT)-guided drain insertion with antibiotic therapy being the current practice.

Research motivation

Complicated spondylodiscitis with IPA formation in immunocompromised patients could be managed in an outpatient setting.

Research objectives

The purpose of the current study was to describe the care management of complicated spondylodiscitis.

Research methods

A 4-year retrospective collection and analysis of all radiologically diagnosed cases of IPA that were treated with CT-guided percutaneous drainage. Data included patient demographics, underlying conditions, isolated microorganisms, antibiotic regimes used, abscess size, days until the withdrawal of the catheter, and final outcome. All draining procedures were performed by direct insertion of a 12 Fr pigtail catheter into the abscess cavity.

Research results

All 8 patients were diagnosed with IPA formation secondary to complicated spondylodiscitis, and two of them were diagnosed with spinal tuberculosis. All 8 patients showed complete recession of the symptoms and radiological findings after the CT-guided abscess drainage and the long-term antibiotic therapy. The microbiology cultures identified *Staphylococcus aureus* in 3 cases and *Mycobacterium tuberculosis* in 2 cases and were negative in the remaining 3 cases. There was no need for patient hospitalization.

Research conclusions

The minimally invasive outpatient management of IPA, which combines CT-guided percutaneous drainage and placement of a drain with proper antibiotic treatment, proved to be a safe and effective approach with a high success rate and low morbidity.

Research perspectives

More studies should be performed in order to prove the cost effectiveness and the decreased morbidity of the minimally invasive outpatient management of these patients.

FOOTNOTES

Author contributions: Fesatidou V wrote the manuscript; Kitridis D reviewed the manuscript, performed a critical revision, and submitted the manuscript; Petsatodis E acquired and analyzed the data; Samoladas E and Givissis P supervised the study and contributed to patient care.

Institutional review board statement: The study was approved by the Institutional Review Board.

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ORIGINAL ARTICLE

Retrospective Study

Direct anterior approach hip arthroplasty: How to reduce complications - A 10-years single center experience and literature review

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Abstract

BACKGROUND

The direct anterior approach for total hip arthroplasty (DAA-THA) is increasing in popularity due to some advantages such as less surgical trauma, minimal dissection of soft tissues, shorter rehabilitation times, faster return to daily activities, lower incidence of dislocation. On the other hand, the literature reports a high rate of intraoperative complications, with many different rates and complication types in the published papers.

AIM

To analyze our complications comparing results with the literature; to report measures that we have taken to reduce complications rate.

METHODS

All DAA-THA patients with one year minimum follow up who were operated at a single high-volume centre, between January 2010 and December 2019 were included in this retrospective study. All surgeries were performed using cementless short anatomical or straight stems and press fit cups. Patients' follow-up was performed, at 6 wk, 3 mo, then annually post-surgery with clinical and radiological evaluation. Primary outcomes were stem revision for aseptic loosening and all-cause stem revision. Second outcome was intra-operative and post-operative complications identification.

RESULTS

A total of 394 patients underwent DDA-THA from January 2010 and December 2019, for a total of 412 hips; twelve patients lost to follow-up and one patient who died from causes not related to surgery were excluded from the study. The

average age at the time of surgery was 61 years (range from 28 to 78 years). Mean follow-up time was 64.8 mo (range 12-120 mo). Seven stems were revised. One cortical perforation, one trochanteric and lateral cortical wall intraoperative fracture, one diaphyseal fracture, three clinically symptomatic early subsidence and one late aseptic loosening. We also observed 3 periprosthetic fractures B1 according to the Vancouver Classification. Other minor complications not requiring stem revision were 5 un-displaced fractures of the calcar region treated with preventive cerclage, one early infection, one case of late posterior dislocation, 18 case of asymptomatic stem subsidence, 6 cases of lateral cutaneous femoral nerve dysesthesia.

CONCLUSION
DAA is associated to good outcomes and lower incidence of dislocation. Complication rate can be reduced by mindful patient selection, thorough preoperative planning, sufficient learning curve and use of intraoperative imaging.

Key Words: Hip arthroplasty; Direct anterior approach; Short hip stem; Minimally invasive surgery; Complications

Core Tip: Direct anterior approach for total hip arthroplasty is increasing in popularity due to some advantages such as less surgical trauma, shorter rehabilitation times, faster return to daily activities, lower incidence of dislocation. Moreover, the literature reports a high rate of intraoperative complications, with many different rates and complication types in the published papers. The aim of this paper is to analyze our complications comparing the results obtained in a total of 412 hips at a mean follow-up of 64.8 mo with those reported in the literature and to describe measures that we have taken to reduce complications rate.

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INTRODUCTION

The direct anterior approach (DAA) was first described by Heuter in 1881 but popularized by Judet starting in 1947[1]. However, it has only recently become popular. In particular, this happened in 2005 following publications by Matta *et al*[2,3]. The increase in popularity of DDA is due to the advantages such as less surgical trauma, minimal dissection of soft tissues, shorter rehabilitation times, faster return to daily activities, lower incidence of dislocation. However, the literature reports a higher rate of perioperative DAA complications than other approaches[4-8] like periprosthetic fracture, prosthesis loosening and nerve injury, but the reported complication rates vary widely in the published literature both in the incidence rate and in the type of complication[9-13]. There is not yet consensus concerning the best approach for total hip arthroplasty (THA) and debates are ongoing[14]. The interest on DAA complications is growing in the recent literature, also compared with those of other hip approaches[15-17]. The aim of our study is to analyze the complication incidence rate in a study group with a maximum follow up of 10 years and compare the results with the literature. Furthermore, from the analysis of our learning curve, we can derive the technical and organizational measures that we have taken to reduce the incidence of complications with the use of DAA for THA.

MATERIALS AND METHODS

All DAA-THA patients with one year minimum follow up who were operated at a single high-volume centre (> 450 arthroplasties/year), between January 2010 and December 2019 were included in this study. The exclusion criteria for the use of DAA in our practice were: age more than 80 years, arthroplasties in hip fractures or in osteolytic lesions, patients with body mass index > 35. Clinical data (gender, age, weight and height) and comorbidities (cardiovascular, respiratory, gastrointestinal, nutritional, endocrine, genitourinary) were collected retrospectively from medical records and outpatient control cards. Radiographic data was taken from the hospital database (Picture archiving and

communication system).

All surgeries were performed using cementless short stems and press fit cup by three surgeons experienced in DAA. Two cementless design of the stem were used. Minimax stem and Versafit press-fit cup (Medacta International, Castel San Pietro, Switzerland) and Fitmore stem and Continuum press-fit cup (Zimmer Biomet, Warsaw, IN, USA). Minimax is anatomically designed, collarless, and made of titanium-niobium alloy (Ti-6Al-7Nb) stem. The neck has a 127 degrees neck-shaft angle with an anteversion of 9 degrees. Minimax stem can be classified as type 6 according to Khanuja *et al*[18] because it is curved, anatomic stems that match the proximal femoral endosteal geometry. Fitmore is a straight designed, tapered, collarless and made of titanium stem which is coated proximally with Ti-VPS (Titanium Vacuum Plasma Spray) and rough-blasted distally. The neck has a neck-shaft angle of 127°, 129°, 137° or 140° without anteversion. Fitmore stem can be classified as type 2 according to Khanuja *et al*[18] because it is a tapered, wedged and proximal porous coated stem that achieves fixation proximally. According to short stem classification[19], Fitmore stem can be classified as type 4, shortened conventional wedged design.

Final decision whether to use DAA was made by the orthopaedic surgeon, in compliance with the exclusion criteria, operating based on age, fragility, bone morphology, and level of activity of the patient. In a same way, decision whether implant straight or anatomical stem was made by orthopaedic surgeon in compliance with proximal femoral anatomy after pre-operative planning[20,21]. Ceramic on ceramic coupling was chosen and 32 mm or 36 mm head diameter were used in all cases.

All surgeries were done in all patients with the support of the standard operating room table or the Amis Mobile Leg positioner (Medacta International, Castel San Pietro, Switzerland).

Primary outcomes were stem revision for aseptic loosening and all-cause stem revision. Second outcome was intra-operative and post-operative complications identification. Patient follow-up was performed at 6 wk, 3 mo and then annually post-surgery.

During preoperative and postoperative radiographic controls, anteroposterior and axial hip radiographs were taken with the foot in a neutral rotational position. Femoral geometries were categorized according to the Door classification system[22] using preoperative anteroposterior radiographs of the hip. The calcar-to-canal ratio was calculated by dividing the canal width, measured at 10 cm below the lesser trochanter, by the calcar width, measured at the middle level of the lesser trochanter. Femurs with a ratio of 0-0.5 were considered type A, 0.5-0.75 as type B, and 0.75-1 as type C [23,24].

Alignment of the stem was considered neutral when the vertical axis of the stem was between 0 and 2° with respect to the femoral shaft axis. A varus-valgus alignment was classified as mild in case of misalignment between 2° and 5° and severe when the misalignment of the stem was greater than 5°. The most recent radiographs were compared to the first postoperative clinic radiographs to evaluate bony remodeling and changes in implant positioning. Stem subsidence was diagnosed in the presence of a stem sinking greater than 3 mm, measured on a perpendicular line drawn from the greater trochanter to the lateral edge of the implant. Implant loosening was diagnosed in the presence of subsidence and/or axial deviation in varus/valgus. We judged early subsidence or axis deviation within 6 mo of surgery, late when observed after 6 mo post-operative.

RESULTS

We retrospectively reviewed a group of 394 consecutive patients who underwent DDA-THA from January 2010 to December 2019 of whom 18 were operated bilaterally in a single procedure, for a total of 412 hips; twelve patients lost to three-month follow-up and one patient who died from causes not related to surgery were excluded from the study. The remaining 381 patients (399 hips) were 263 (65.9%) female and 136 (34.1%) male. The average age at the time of surgery was 61 years (range from 28 to 78 years). The preoperative diagnosis was primary osteoarthritis in 328 cases (14 bilateral), avascular necrosis of the femoral head in 38 cases (3 bilateral), rheumatoid arthritis in 11 cases (1 bilateral), traumatic osteoarthritis in 18 cases, and other causes in 4 cases. Demographic data of patients are sumarized in Table 1. Mean follow-up time was 64.8 mo (range 12-120 mo). In 238 cases an anatomical stem was used, in 161 cases a straight stem was used. Three hundred forty-four surgeries were performed *via* the DAA using a standard operating room table (86.2%) and 44 (13.8%) surgeries were performed using the AMIS mobile leg.

Seven stems were revised. One cortical perforation was observed on postoperative radiographic control and then revised. One trochanteric and lateral cortical wall fracture was intraoperative observed and fixed with cerclage and stem revision. One diaphyseal fracture was treated by plate fixation. Three clinically symptomatic early subsidence revised respectively 5, 6 and 7 mo after surgery. One aseptic loosening 4 years after surgery (Figure 1). We also observed 3 periprosthetic fractures B1 according to the Vancouver Classification. The intra operative complications observed, in addition to the cortical perforation, the diaphyseal fracture and the trochanteric fracture, were 5 un-displaced fractures of the calcar region treated with preventive cerclage (Figure 2). One early infection was treated with surgical washing and head and liner revision followed by antibiotic therapy. One posterior dislocation was

Table 1 Demographic data of patients

Parameters	Values
No. of patients	381
No. of hips	399
Gender (male/female), *n* (%)	136 (34.1)/263 (65.9)
mean age (yr)	61 (28-78)
mean follow-up (mo)	64,8 (12 –120)
Diagnosis (No. hips)	
Osteoarthritis	328 (14 bilateral)
Avascular necrosis	38 (3 bilateral)
Rheumatoid arthritis	11 (1 bilateral)
Traumatic osteoarthritis	18
Other causes	4
Surgical technique, *n* (%)	
Standard operating room table	445 (86.4)
AMIS mobile leg positioner	54 (19.4)

observed one year after surgery (Figure 3). Patient referred dislocation during a squat on the ground with the loss of balance. Dislocation was reduced without anesthesia, no further dislocations were observed one year after reduction. Six patients referred numbness or paresthesias within the cutaneous distribution of the anterolateral thigh at follow-up.

According to Dorr classification[17], 168 hips (42%) were graded as Dorr A, 192 hips (48%) as Door B and 39 hips (10%) as Dorr C. In our experience pre-operative planning showed more suitable Fitmore stem for a femoral geometry type A (84/168), according to the Door classification system. This is due to the tapering of the tip adaptable to a narrow femoral canal. Minimax stem is instead more suitable for a femoral geometry type C due to more filling metaphyseal portion (37/39). For this reason, the two groups of patients treated with Fitmore stem and Minimax stem appear not homogeneous and their incidence of complications is not comparable.

In 307 (77%) cases the alignment of the stem was considered neutral, in 76 (19%) cases it was considered mild varus-valgus and in 15 (4%) cases severe varus-valgus. Trabeculae hypertrophy was observed in 84 cases (21%) at zone 3, in 45 cases (11%) at zone 5 and 5 cases (2%) at zone 4. There was grade 1 stress shielding (calcar round-off) in 5 cases (2%). No hypertrophy at zones 8-14 (lateral view) were observed. Stem subsidence > 3 mm, in addition to the one symptomatic case revised, was observed 4 more times (4 mm, 7mm, 6 mm and 10 mm respectively). In all these 4 cases, the absence of pain and the tolerated leg length discrepancy did not compromise the good final functional result.

Finally, 445 (86.4%) surgeries (11 bilateral) were performed *via* the DAA using a standard operating room table and 54 (19.4%) surgeries (7 bilateral) were performed using the Amis Mobile Leg. Comparison between demographic characteristics and the incidence of complications in the two patient groups (anatomical and straight stem) did not reveal significant differences (Table 2).

DISCUSSION

This study was undertaken to evaluate DAA-THA complication rates. For this reason, we retrospectively evaluated clinical and radiographic complications at a mean follow-up of 64.8 mo (range 12-120 mo) in 381 patients (399 hips). All patients received a cementless anatomical short stem or a tapered wedged short stem according to inclusion criteria.

Incidence of dislocation is certainly the most relevant result of our study. Commonly considered to be lower than that of others approaches, the small dislocation rate of the DAA is one of the reasons for the great popularity of this approach, although a widely accepted consensus has not been reached yet and some authors report higher complication rates[25].

We found one case of hip dislocation on 399 hips (0.2%) (Figure 3), which represents the one of the lower dislocation incidences reported in literature in case of large study group[26], with the latest works reporting dislocation rate from 0.23% to 2.5%[27,28].

Table 2 Major and minor complications

Complications	Anatomical stem (*n* = 238)	Straight stem (*n* = 161)
Major complication (with stem revision)	6	4
Acute mobilization	1	1
Trochanter fracture	-	2
Diaphyseal fracture	1	-
Aseptic loosening	1	-
Subidence	1	-
Periprosthetic fractures	2	1
Minor complication	18	9
Calcar fractures (Intraoperative cerclage)	5	1
Ossification	-	1
Subsidence		
Conservative treatment ≤ 3 mm	9	5
Conservative treatment > 3 mm	3	1
Dislocation	-	1
Early infection	1	-
LCFN dysesthesia	4	2

LCFN: Lateral cutaneous femoral nerve.

Unexpectedly, the case of hip dislocation found in our study was a posterior dislocation occurred after hip hyper-flexion and adduction, factually suggesting an inadequate cup anteversion, since the dislocation after THA performed with the DAA is usually anterior also due to the preservation of the musculo-tendinous attachments of the short external rotators which are important for hip stabilization after arthroplasty. Nevertheless, also Barnett *et al*[27] reported a prevalence of posterior dislocation.

Acetabular cup anteversion and inclination are a key point for the long-term success of THA and seen as a challenge in DAA-THA. There are some studies suggesting alternative solutions on this issue; Hu *et al*[29] described satisfactory clinical and radiographic outcomes achieved by DAA-THA performed in the lateral position. Fluoroscopic guidance is reported to be used to improve component positioning during anterior approach THA, but with still debated results; for example, Rathod *et al*[30] depicted a reduction of variability of acetabular cup anteversion using fluoroscopy with the patient in the supine position during direct anterior THA, while Kobayashi *et al*[31] revealed potential excessive cup anteversion and flexion implantation of the stem obtained from fluoroscopic assistance by surgeons in their early experience with DAA. In our practice, we do use intraoperative imaging, but especially to check stem size and alignment in order to mitigate the tendency to undersize the femoral implant associated to DAA-THA, as described in our previous work[32].

Although the use of different femoral heads size has been described in many studies[33,34], it's known that the use of larger femoral heads increases the head-neck ratio and consequently increases the range of movement before reaching the point of primary impingement thus reducing dislocation rates, as reported in the published literature[35-37]. Also aware of this, in our series we used only 32 mm or 36 mm diameter heads.

An analysis of the Norwegian Arthroplasty Register found overall similar revision rates between hip approaches, but the posterior approach was associated with more than twice the risk of revision due to dislocation when compared with alternate approaches[38].

In the literature are reported various revision rates, rising from 0%[39] to 3.3%[28] with different follow up time. In our series, the global revision rate was 1.8% and revision rate for aseptic loosening was 1% at a mean follow up of 65 mo, with particular attention to three clinically symptomatic early subsidence revised respectively 5, 6 and 7 mo after surgery; especially in these cases it is critical, in our opinion, the intraoperative imaging to mitigate the tendency to undersize the femoral implant associated to DAA-THA[32].

The risk of intraoperative fractures is due to the difficult exposure of the femur. Early studies reported a high complication rate with the use of a fracture table[40]. Most of these were avulsions of the greater trochanter. The evolution of specialized traction tables for DAA, promoting greater patient hip positioning than patient hip traction, has reduced the incidence of complications. Although the

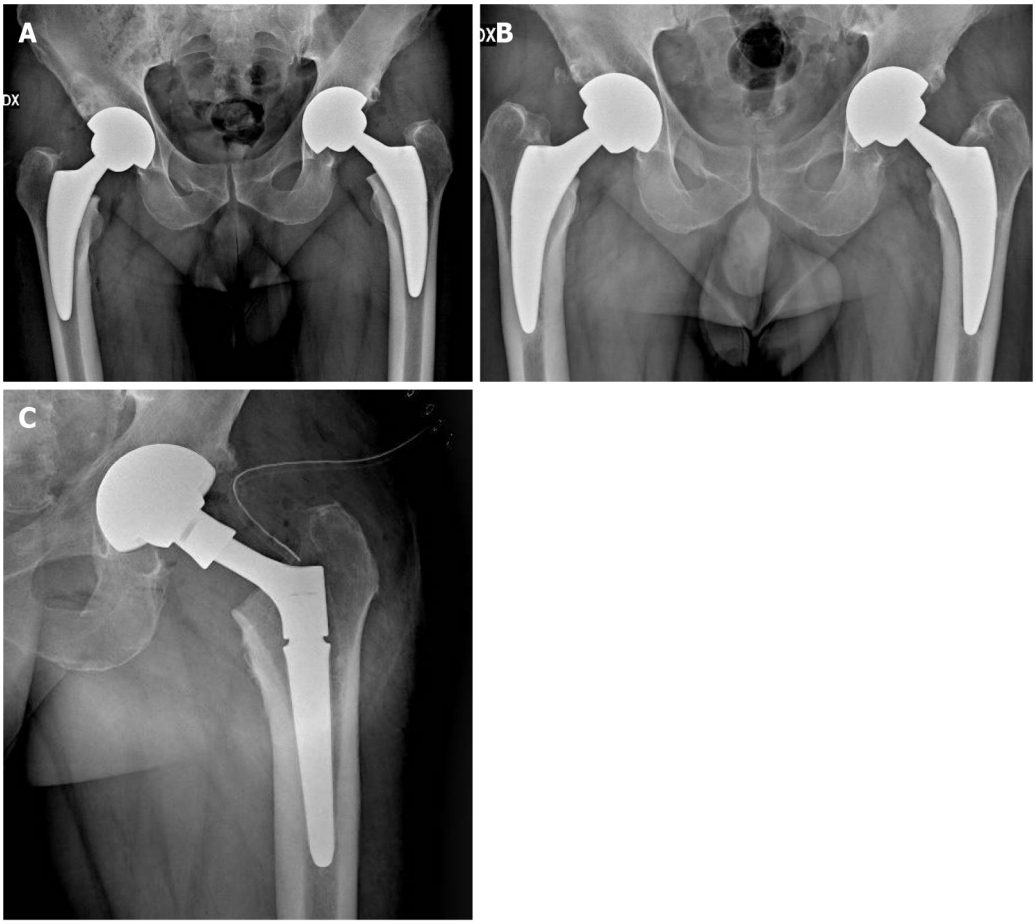

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Figure 1 A 55 years old man undergone bilateral one-stage direct anterior approach for total hip arthroplasty. A: Postperative X-ray control; B: Radiological evidence of left femoral stem loosening after 4 years from the surgery; C: Revision of the loosed femoral stem.

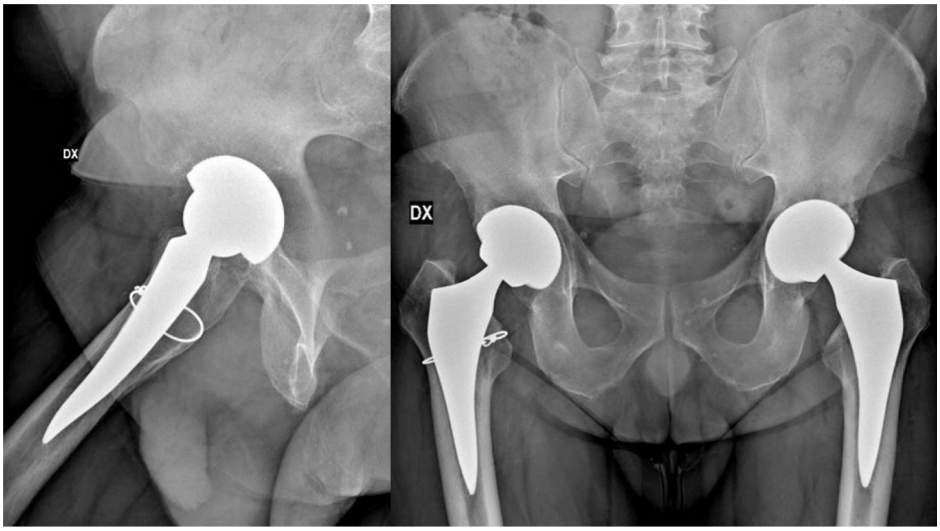

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Figure 2 A 48 years old man undergone bilateral one-stage direct anterior approach for total hip arthroplasty; intraoperative right femur cerclage due to calcar incomplete fracture.

differences between complications during the traction table or the standard table are still debated in the current literature, the incidence of intraoperative fracture in DAA is reported between 1.3% and 2.4% [41-43]. The use of short femoral stems is described as a reduction in the risk of intraoperative fractures [44-46]. Dietrich *et al*[44] reported a significantly reduced fracture rate of 1.6% *vs* 6.8% in 457 DAA with

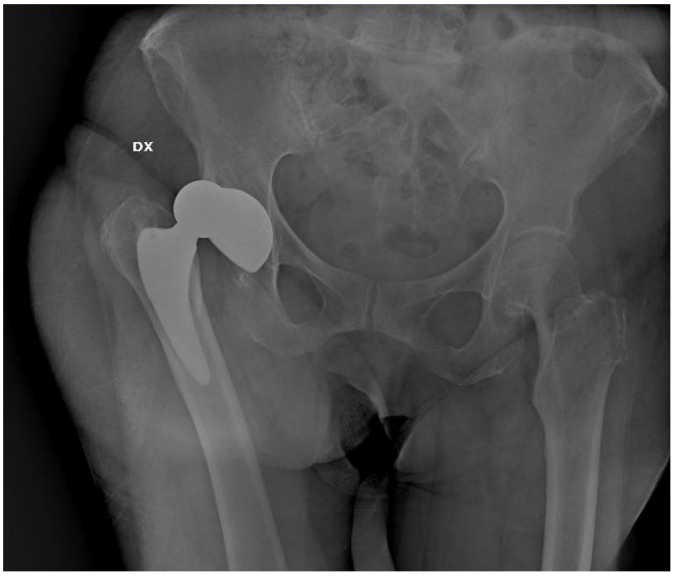

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Figure 3 Posterior hip dislocation in 80 years old woman one year after direct anterior approach for total hip arthroplasty.

conventional straight stems. Luger *et al*[45] reported 0.9% of intraoperative fractures after 1052 DAA-THA with the same straight stem used in our study. In our opinion, the use of short stems with specific instruments for DAA favors the introduction into the femoral canal, decreases the points of conflict with cortices during introduction and decreases the incidence of complications. We observed 3 major complications (0.7%) related to intraoperative fractures (Figure 4). Our rate of intraoperative fracture increases to 2% including minor complications (intraoperative cerclages due to calcar incomplete fractures). Our results encourage us to continue our experience with short stems, both with the use of the standard table and the traction table[8]. Surprisingly, however, Greco *et al*[42] report an opposite experience. They observed higher femoral complications (1.27%) with short stem standard profile as compared to full length standard profile (0.77%). The Authors concluded that short stem may impart greater stress concentration in the proximal femur during broaching and stem insertion which could increase the risk of fracture. On the contrary, a longer stem aids with the direction of broaching and may prevent inappropriate contact against the femoral cortices. One of the Authors has decided to avoid use of the short stem option in elderly female patients given the compounded risk of femoral complication.

Despite DAA utilizes an internervous plane between Tensor fasciae lata and Gluteus medius muscles (Superior gluteal nerve) and Sartorius and Rectus femoris muscles (Femoral nerve), nerve complications are however possible.

Injury to lateral cutaneous femoral nerve (LCFN) is a not rare minor complication. LCFN is a pure sensory nerve is a sensory nerve that forms from the roots of L2 and L3; travels along the posterolateral aspect of the psoas e iliac muscles through the anterosuperior iliac spine, ending superficially at the sartorius muscle. Then LCFN pierces the fascia lata beneath the inguinal ligament and runs laterally and distally within the subcutaneous tissue of the anterolateral region of the thigh. Some authors describe a division of the LFCN into an anterior (femoral) and posterior (gluteal) branch after passing behind or through the inguinal ligament. Rudin *et al*[47] classified the branching pattern of the LFCN in three as Sartorius-type (dominant anterior branch on the lateral border of the Sartorius muscle and further branches in the anterior aspect of the thigh), posterior-type [strong posterior branch equal in thickness to, or thicker than, the anterior branch. It runs laterally and crosses the medial border of the tensor fascia lata (TFL) muscle distal to the anterior superior iliac spine (ASIS)] or fan-type (multiple nerve branches of equal thickness on the anterolateral region of the proximal aspect of the thigh, crossing over the TFL and the lateral border of the Sartorius). They reported 36% of sartorius-type, 32% of posterior-type and 32 of fan-type after dissection of twenty-eight cadaveric hemipelves from 18 donors. In contrast to this data, Thaler *et al*[48], after a study on 44 Limbs and hemipelves from 22 formalin-preserved cadavers, showed a Sartorius-type branch pattern (70.5%) of the LFCN in the majority of cases, while a posterior-type and a fan-type were detected in 13.6% and 15.9% of cases, respectively. If these data were confirmed, injury to branches of the LFCN should be avoided in most cases by a skin incision 2 cm lateral to the ASIS end its distal extension as lateral as possible.

The true incidence of this complication remains unclear. The reported incidence in literature ranges from 0.1% to 81%. This is due to both the diagnostic difficulty and the degree of accuracy of the clinical examination at follow up. In fact, symptoms ranging from hypoesthesia to painful paresthesias and there is no validated diagnostic tool for LFCN neuropraxia. Patients with LFCN injury often report numbness, paresthesias, or even dysesthesias analogous to meralgia paresthetica within the cutaneous

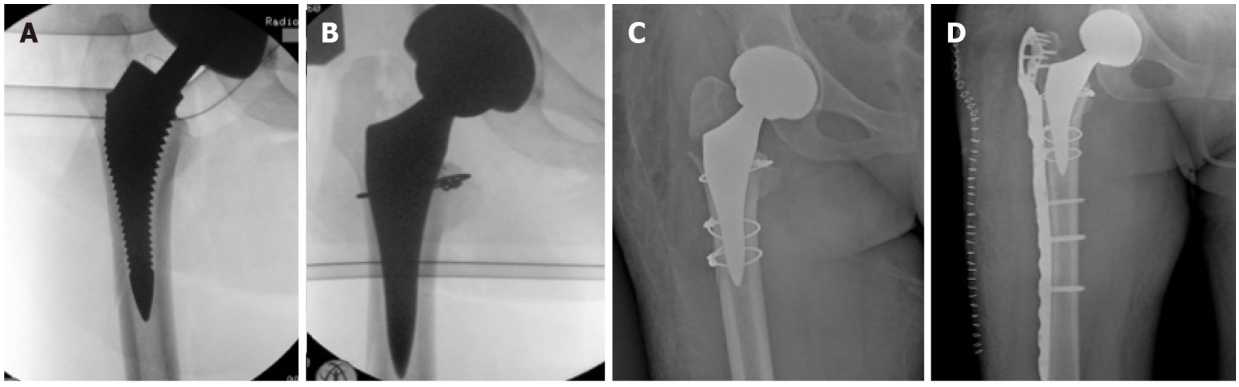

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Figure 4 A 61 years old woman undergone direct anterior approach for total hip arthroplasty. A, B: Lateral femoral wall fracture showed at intraoperative control and then fixed with cerclage; C: Evidence of undiagnosed trochanteric fracture at postoperative control; D: X-rays control after periprosthetic plate and screws.

distribution of the anterolateral thigh. In our experience, patients often do not report dysesthesia during postoperative follow-up. The disorder is in fact reported only if the patient is directly questioned about the problem of skin sensitivity. Only in 6 cases patients did report dysesthesia or numbness as a symptom that occasionally caused discomfort. We did not include direct skin sensitivity assessment forms in our follow-up, this is a possible reason of our low incidence (1.5%) of LCFN injury. Homma *et al*[49] investigating skin sensitivity problems using a dedicated questionnaire, showed 31.9% of LFCN injury. In the same way Patton *et al*[50] reported numbness in 37% of patients with decreasing of incidence to 11% of patients from 6-8 years post op. The fact that symptoms related to LCFN lesion are often reported only after a specific question further suggests that it is a minor complication. Furthermore, in most cases, the presence of LCFN lesions appears to be independent of hip function scores and does not affect final result.

The superior gluteal nerve is a motor nerve, which is formed from the roots of L4 and L5 and the first sacral spinal nerves that supply the gluteus medius, gluteus minimus, and TFL muscles. It runs sideways between the gluteus medius and minimus and then divides into upper and lower branches. Both the upper and lower branches innervate the gluteus medius and minimal muscles. Furthermore, the terminal branches of the inferior branch run anteriorly and supply the tensor of the fascia lata. Precisely these terminal branches represent the anatomical structure at risk. Overstretching the TFL muscle using retractors during surgery or coagulation of the near ascending branch of the lateral circumflex femoral artery can be causes of Injury. There is little information in the literature regarding injury to the TFL with respect to the DAA[51]. The consequences of atrophy of the tensor fasciae are cosmetic, but potential functional deficit is unknow.

Even if in our study we did not consider blood loss, it is reported that DAA THA is related to lower intraoperative blood loss and smaller changes in pre- and postoperative hemoglobin values, less blood drained, and lower volumes of blood transfusions required[52]. Moreover, Zhao *et al*[53] described no statistically significant differences in the rate of blood transfusion, hematoma, or re-bleeding between patients undergone ligation of the branches of the lateral circumflex femoral artery pedicle *vs* those treated with electrocautery.

There are some uncommon complications that are still to be taken into account; Hogerzeil *et al*[6] reported the case of a 69-year-old male patient who developed acute compartment syndrome of the thigh after elective DAA THA while using therapeutic low molecular weight heparin as bridging for regular oral anticoagulation. Also the risk of excessive radiation exposure to both the patients and the surgeons has to be considered; Jinnai *et al*[54] compared the intraoperative fluoroscopy time of DAA-THA with that of osteosynthesis for proximal femoral fracture to determine if the level of radiation exposure exceeded safety limits and concluding that the intraoperative exposure level was significantly lower and the fluoroscopy time was significantly shorter in DAA-THA than in osteosynthesis.

There are some limitations in this paper. First, the main weakness of our work is the retrospective design of the study. Second, we did not include direct skin sensitivity assessment forms in our follow-up controls and this could be a possible reason of our low incidence of LCFN injury. Third, the exclusion of ages of more than 80 could be considered a selection bias, improving clinical outcome and reducing the revision rate. Fourth, we did not use radiostereometric analysis to evaluate for stem subsidence, but only manual techniques of measurement.

CONCLUSION

DAA is associated to less surgical trauma, minimal dissection of soft tissues, lower blood loss, shorter rehabilitation times and lower incidence of dislocation. Complication rate can be reduced by mindful patient selection, preoperative planning with proper implant choice, sufficient learning curve, use of intraoperative imaging to check cup and stem orientation and to mitigate the tendency to undersize the femoral implant.

ARTICLE HIGHLIGHTS

Research background

The direct anterior approach for total hip arthroplasty (DAA-THA) is increasing in popularity due to some advantages such as less surgical trauma, minimal dissection of soft tissues, shorter rehabilitation times, faster return to daily activities, lower incidence of dislocation with different reports in the published papers.

Research motivation

Some literature reports a high rate of perioperative complications, with many different rates and complication types among the published papers without reaching a clear consensus.

Research objectives

Objectives of our study are to analyze our complications and comparing results with the literature reports and to report measures that we have taken to reduce complications rate.

Research methods

We retrospectively collected data of all DAA-THA patients with one year minimum follow up who were operated at a single high-volume centre, between January 2010 and December 2019. All surgeries were performed using cementless short anatomical or straight stems and press fit cups. Patients' follow-up was performed with clinical and radiological evaluation. Primary outcomes were stem revision for aseptic loosening and all-cause stem revision. Second outcome was intra-operative and post-operative complications identification.

Research results

The authors collected 394 patients underwent DDA-THA from January 2010 and December 2019, for a total of 412 hips; twelve patients lost to follow-up and one patient who died from causes not related to surgery were excluded from the study. Mean follow-up time was 64.8 mo (range 12–120 mo). Seven stems were revised. One cortical perforation, one trochanteric and lateral cortical wall intraoperative fracture, one diaphyseal fracture, three clinically symptomatic early subsidence and one late aseptic loosening. We also observed 3 periprosthetic fractures B1 according to the Vancouver Classification. Other minor complications not requiring stem revision were 5 undisplaced fractures of the calcar region treated with preventive cerclage, one early infection, one case of late posterior dislocation, 18 case of asymptomatic stem subsidence, 6 cases of lateral cutaneous femoral nerve dysesthesia.

Research conclusions

In our experience DAA is associated to good outcomes and lower incidence of dislocation. According to our results complication rate can be reduced by mindful patient selection, thorough preoperative planning, sufficient learning curve and use of intraoperative imaging.

Research perspectives

Despite these good results, the choice of the ideal surgical approach of THA is still controversial and studies on larger samples are needed.

FOOTNOTES

Author contributions: All authors gave substantial contributions to conception and design of the study, acquisition of data, or analysis and interpretation of data, drafting the article and making critical revisions related to important intellectual content of the manuscript and final approval of the version of the article to be published.

Institutional review board statement: The study and follow-up, respecting the criteria of the Declaration of Helsinki, were approved by the ASN/Sav Institutional Review Board.

Informed consent statement: In this retrospective analysis we used anonymous clinical data that were obtained after each patient agreed to treatment by written consent form; all patients accepted the proposed treatment and follow-up after adequate information and gave written consent. For full disclosure, paper copy is available at SS Annunziata Hospital, Savigliano, Italy.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to this study.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at rivgio@libero.it. The presented data are anonymized and risk of identification is very low.

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ORIGINAL ARTICLE

Retrospective Study

Integrity of the hip capsule measured with magnetic resonance imaging after capsular repair or unrepaired capsulotomy in hip arthroscopy

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Abstract

BACKGROUND

Current literature shows no clear answer on the question how to manage the capsule after hip arthroscopy. Regarding patient reported outcome measures there seems to be no difference between capsular repair or unrepaired capsulotomy.

AIM

To evaluate and compare the integrity of the hip capsule measured on a magnetic resonance imaging (MRI) scan after capsular repair or unrepaired capsulotomy.

METHODS

A case series study was performed; a random sample of patients included in a trial comparing capsular repair *vs* unrepaired capsulotomy had a postoperative MRI scan. The presence of a capsular defect and gap size were independently evaluated on MRI.

RESULTS

A total of 28 patients (29 hips) were included. Patient demographics were comparable between treatment groups. There were 2 capsular defects in the capsular repair group and 7 capsular defects in the unrepaired capsulotomy group (P = 0.13). In the group of patients with a defect, median gap sizes at the acetabular side were 5.9 mm (range: 2.7-9.0) in the repaired and 8.0 mm (range: 4.5-18.0) in the unrepaired group (P = 0.462). At the muscular side gap sizes were 6.6 mm (range: 4.1-9.0) in the repaired group and 11.5 mm (range: 3.0-18.0) in the unrepaired group (P = 0.857). The calculated Odds ratio (OR) for having a capsular defect with an increasing lateral center-edge (CE) angle was 1.12 (P = 0.06). The OR for having a capsular defect is lower in the group of patients that underwent a labral repair with an OR of 0.1 (P = 0.05).

CONCLUSION

There is no significant difference in capsular defects between capsular repair or unrepaired capsulotomy. Regarding clinical characteristics our case series shows that a larger CE angle increases the likelihood of a capsular defect and the presence of a labral repair decreases the likelihood of a capsular defect.

Key Words: Hip; Arthroscopy; Magnetic resonance imaging; Capsule; Thickness

Core Tip: In this case series we evaluated the integrity of the hip capsule after hip arthroscopy with a magnetic resonance imaging scan and compared between patients in a capsular repair group and unrepaired capsulotomy group. The magnetic resonance imaging scan of 29 hips was observed to determine whether there was a capsular defect or not. After 12 mo follow-up no difference was found between groups regarding the presence of a capsular defect or not.

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INTRODUCTION

Hip arthroscopy is a more and more popular technique to address intra-articular pathology of the hip[1,2]. Entrance to the hip is made by several portals and usually an interportal or T-shaped capsulotomy is performed to improve workspace in the joint[3]. In the early days of hip arthroscopy these capsulotomies were usually left unrepaired[4]. In recent years there has been debate on what to do with the capsulotomy at the end of the procedure. Some papers suggest that routine capsular closure might result in improved outcomes after surgery where other papers report conflicting evidence and show no superiority of routine capsular repair[5-10]. However, there are cadaveric studies that show the biomechanical importance of complete capsular repair[11,12]. Restoration of the hip joint capsule results in hip joint kinematics to near normal levels after interportal or T-shaped capsulotomy[12]. The unrepaired hip capsulotomy might be a reason for developing postoperative iatrogenic hip instability[13,14]. As the (un)repaired capsulotomy might be a contributor to postoperative complaints of patients with iatrogenic hip instability, this may be quantified by assessment of the quality and morphologic appearance of the hip capsule with magnetic resonance imaging (MRI)[15].

The purpose of this study is to evaluate the integrity of the hip capsule after capsular repair or unrepaired capsulotomy measured with MRI. Our secondary aim is to evaluate the association between pre- and perioperative details and the quality and integrity of the capsule.

MATERIALS AND METHODS

Study design and participants

For the current study a random sample of 28 patients (29 hips) with residual hip complaints after surgery or complaints of the contralateral hip had an MRI scan postoperatively and were enrolled in the current study. All patients were part of a trial that was designed and approved after local medical ethical committee approval (NL55669.048.15). Inclusion criteria for the trial were age between 18-65 years, a body mass index (BMI) lower than 35 and good understanding of Dutch/English language and with intra-articular hip pathology who opt for hip arthroscopy. Exclusion criteria were revision hip arthroscopy, extra-articular hip pathology, a documented systemic connective tissue disease or hypermobility, a center-edge (CE) angle of less than 25 degrees, prior hip surgery or a hip fracture in the past. After randomization patients were either allocated to repaired capsulotomy or the unrepaired capsulotomy group. All patients were operated by the senior author. Functional outcome was measured at baseline and after 12 mo follow-up with the Copenhagen Hip and Groin Outcome Score (HAGOS) [16].

The postoperative MRI scans were independently evaluated for capsular integrity by Bech NH and Haverkamp D to assess inter observer reliability. Both authors were blinded to clinical and detailed operative information to prevent bias.

Final cohort consisted of 29 hips (28 patients) of which 16 were in the unrepaired group and 13 in the capsular repair (repair) group that had received a postoperative MRI scan.

Surgical technique

Patients were operated *via* standard technique and 2 or 3 portals were made. An interportal capsulotomy was done in all patients. No T-shaped capsulotomies were done. Repair of the capsule took approximately 15 min of operating time. The capsular repair was done with 2 or 3 sutures by arthroscopic technique (Capsular Close Scorpion, Arthrex). Standard sutures were used (Fibrewire, Arthrex).

Postoperative protocol

In both groups the rehabilitation protocol was similar. The first 4 wk no weight bearing was allowed. After that, patients started weight bearing with crutches. From week 5 till week 12 patients started with passive and active exercises and were guided by a physiotherapy. After week 12 there were no more restrictions. All patients received standard 4 wk of non-steroid anti-inflammatory drugs (diclofenac) to inhibit heterotopic ossification.

Capsular quality assessment on MRI

The used technique for measuring capsular defects has been previously described in the paper of Strickland *et al*[17]. Capsular integrity was measured on a proton weighted density sequence or the T2 weighted fat-saturated sequence in the coronal plane. First step was to determine if there was a capsular defect (Figure 1). The definition of a capsular defect was described by Weber *et al*[18]; being any visual disruption of the iliofemoral ligament or any appearance of communication between the joint and the iliofemoral bursa seen with contrast (Figure 1A and B)[18]. Furthermore, we measured 2 parameters: Gap length on the acetabular side and the gap length on the muscular side of the defect (Figure 1A and B)

Statistical analysis

Patient and clinical characteristics are described as means ± SD in case of normally distributed continuous variables. Otherwise, medians with ranges are presented. Comparisons between repair groups were performed by use of *t*-tests or non-parametric Mann Whitney *U*-tests where appropriate. Categorical variables are presented as numbers with accompanying proportions and analyzed by use of χ^2 tests or Fischer Exact-tests (in case of expected numbers < 5). For the presence of a capsular gap, absolute agreement was calculated to present inter observer reliability. The association between pre- and perioperative details and the presence of a defect was analyzed by use of a univariate logistic regression analysis and Odds ratios (OR) with 95%CI were calculated. Intra class correlation coefficients ($ICC_{agreement}$, 2-way random effect model) were calculated for both acetabular and muscular gap length. A P value < 0.05 was considered statistically significant.

Analysis was performed by use of SPSS statistical software (IBM Corp. IBM SPSS Statistics for Macintosh Version 26.0. Armonk, NY: IBM Corp).

RESULTS

Patient demographics

The mean age in the unrepaired group was 33.3 ± 6.1 and in the repair group 31.4 ± 9.1. Average follow-

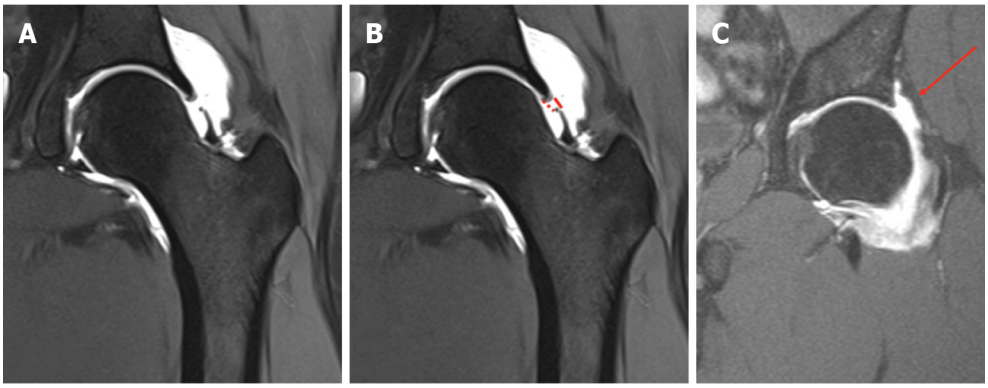

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Figure 1 Example of capsular defect and intact capsule on magnetic resonance imaging-arthrography. A: example of a capsular defect on magnetic resonance imaging (MRI)-arthrography with extracapsular contrast leakage to the adjacent soft-tissue; B: Gap length measurement; solid line: gap length muscular side. Dotted line: Gap length acetabular side; C: Example of an intact capsule on MRI-arthrography (Arrow). There is no contrast leakage to the adjacent soft-tissue.

up in the repair group was 15.8 ± 6.5 mo and in the unrepaired group 12.6 ± 6.7 mo. Regarding baseline characteristics there were no significant differences between both groups (Table 1).

Regarding the HAGOS functional outcome score both baseline and 12 mo follow-up values are given in Table 2. In the capsule defect group, 7 patients reached the 12 mo follow-up, in the capsule intact group, 16 patients reached the 12 mo follow-up. Between the capsule intact and the capsular defect group, there were no differences on all 5 domains of the HAGOS outcome score (Table 2).

Capsular defects

In total there were 9 capsular defects measured on MRI, 20 hips did not have a capsular defect. For the assessment of the presence of capsular defect there was 100% agreement between observers. In the repair group, there were 2 patients (15.4%) with a measurable capsular defect on MRI, and in the unrepaired group 7 patients (43.8%) (P = 0.13).

In the capsular repair group, there were 2 failures. The first was a 23-year-old woman with a large CE angle (44 degrees) and a BMI of 24,6. The second patient was a 45-year-old woman with a hip that had already some signs of osteoarthritis, a CE angle of 36.9 degrees and a BMI of 33.3.

Gap size

Inter observer reliability of gap size measurements was good to excellent with ICC values of 0.83 and 0.94 of the gap measurements at the acetabular and muscular side.

Among patients with a capsular defect, median gap sizes at the acetabular side were 5.9 mm (range: 2.7-9.0) and 8.0 mm (range: 4.5-18.0) in the repaired and unrepaired group, respectively (P = 0.462). At the muscular side, gap sizes were 6.6 mm (range: 4.1-9.0) and 11.5 mm (range: 3.0-18.0), respectively (P = 0.857).

Clinical characteristics and capsular defect

Although not significant patients with a larger CE angle were more likely to have a capsular defect on MRI with an OR of 1.12 (P = 0.06).

In the group of patients with a capsular defect, there were 2 with a CAM-type deformity and 5 with a pincer-type deformity. In the capsule intact group, there were 6 patients with a CAM-type deformity and 9 patients with a pincer-type deformity. There was no significant association between the presence of a CAM or pincer deformity and a capsular defect (Table 3).

In the capsular defect group, there was 1 patient that underwent a labral repair; in the capsule intact group, 11 patients underwent a labral repair. Patients with a labral repair were less likely to have a capsular defect on MRI with an OR of 0.1 compared to patients without labral repair (P = 0.05) (Table 3).

DISCUSSION

In this case series we found that the incidence of a capsular defect, although not significant, was higher in the unrepaired capsulotomy group than in the repaired group. Our results are comparable to available current literature. In the randomized controlled trial of Strickland *et al*[17] they investigated 30 hips and compared capsular closure *vs* unrepaired interportal capsulotomy during simultaneous bilateral arthroscopy. They measured the capsular defect and the quality of the capsule postoperatively

Table 1 Patient demographics

	Repaired (*n* = 13)	Unrepaired (*n* = 16)	*P* value
Sex			0.36
Male	4 (30.8)	2 (12.5)	
Female	9 (69.2)	14 (87.5)	
BMI	23.8 ± 3.9	23.1 ± 2.3	0.67
Age (yr)	31.4 ± 9.1	33.3 ± 6.1	0.49
Follow-up (mo)	15.8 ± 6.5	12.6 ± 6.7	0.72
Impingement type			
CAM	5 (38.5)	3 (18.8)	0.62
Pincer	5 (38.5)	9 (56.3)	0.34
Labral repair	5 (38.5)	7 (43.8)	0.22
CE angle at time of MRI (degrees)	38.2 ± 7.7	34.0 ± 9.8	0.48

Data are presented as *n* (%) or mean ± SD. BMI: Body mass index; CE: Center-edge; MRI: magnetic resonance imaging.

Table 2 Hip and Groin Outcome Score functional outcome score at baseline and after 12 mo follow-up

	Capsular intact (*n* = 20)	Capsular defect (*n* = 9)	*P* value
Baseline			
HAGOS, median (IQR)			
Symptoms	44.6 (35.7-58.9)	35.7 (28.6-37.5)	0.08
Pain	43.8 (32.5-54.4)	35.0 (31.3-48.8)	0.39
ADL	47.5 (26.3-65.0)	40.0 (40.0-67.5)	0.84
Sport	32.8 (19.5-43.0)	25.0 (19.5-37.5)	0.71
QoL	25.0 (15.0-35.0)	25.0 (21.3-38.8)	0.64
12 mo FU			
HAGOS, median (IQR)			
Symptoms	51.8 (32.1-74.1)	39.3 (35.7-64.3)	0.82
Pain	70.0 (48.8-86.3)	60.0 (40.0-92.5)	0.87
ADL	67.5 (40.0-90.0)	60.0 (50.0-95.0)	0.62
Sport	53.6 (25.8-80.5)	53.1 (35.7-81.3)	0.87
QoL	40.0 (26.3-53.8)	60.0 (40.0-60.0)	0.28

HAGOS: Hip and Groin Outcome Score; IQR: Interquartile Range; FU: Follow-up; ADL: Activity of daily living; QoL: Quality of life.

and report no significant differences between treatment groups at final endpoint at 24 wk after surgery. Kraeutler *et al*[19] performed a multicenter randomized trial between capsular repair and unrepaired capsulotomy. They also report no differences between both treatment groups regarding healing of the capsule measured on MRI[19].

In the paper of Weber *et al*[18] symptomatic patients were evaluated with MRI after capsular repair. They reported that 1 year after surgery 92.5% of the repaired capsules remained closed and that the capsule was thickened at the site of the repaired capsulotomy compared to the unaffected contralateral hip capsule[18].

To our best knowledge there is no literature that investigated the association between the size of the CE-angle and the presence of a capsular defect. In our series the likelihood of a capsular defect was larger with an increasing CE angle. An explanation for this finding could be that in this group the incidence of pincer impingement was higher. As part of the procedure of pincer impingement the surgeon must resect a part of the acetabulum and detach a part of the iliofemoral ligament. Extended

Table 3 Association between clinical characteristics and presence of a capsular defect

	OR (95%CI)	*P* value
CE angle at time of MRI	1.12 (1.00-1.26)	0.06
CAM	0.67 (0.11-4.20)	0.67
Pincer	1.53 (0.31-7.44)	0.60
Labral repair	0.10 (0.01-0.98)	0.05

CE: Center-edge; MRI: magnetic resonance imaging.

resection and concomitant ligament damage could lead to possible higher incidence of capsular defects after surgery. In our series there were only 2 failures in the capsular repair group that showed a capsular defect on MRI. Possibly the rather large CE angle in both patients was of influence and led to subsequent failure of capsular healing.

Regarding labral repair there was a significant larger portion of patients with an intact capsule in the labral repair group. It is unsure where the difference in capsular defects between labral repair and no repair originates from. A possibility is that more stability from a repaired labrum influences the capsular healing. Cadaveric studies show that an intact labrum absorbs a lot of strain during motion of the hip [20]. Without the intact labrum the hip capsule might have to compensate for these forces resulting in possibly a higher incidence of capsular defects.

Strengths

A strength of this study is that the capsular defect was measured by two authors separately and that an intra classifier coefficient was calculated to verify the accuracy of the measured defects.

Limitations

The first limitation of this study is that small number of patients were included. We expect that although there was a clinically relevant difference in measurable defect between the groups, this difference was not statistically different because of the small sample size. Secondly, only symptomatic patients or patients with complaints of the contralateral hip had an MRI scan and this could have introduced a bias in our results.

CONCLUSION

Our current study shows that there is no significant difference in capsular healing on MRI between capsular repair or unrepaired capsulotomy. Furthermore, a higher CE angle increases the likelihood of having a capsular defect and the presence of a labral repair decreases the likelihood of a capsular defect. Although there seems to be no reason for routinely capsular closure after hip arthroscopy, knowing these patient specific factors might help the orthopedic surgeon to decide to perform a capsular repair in specific cases.

ARTICLE HIGHLIGHTS

Research background

Capsular management after hip arthroscopy remains topic of debate after an interportal capsulotomy

Research motivation

More studies are needed to determine what the effect is of capsular repair on capsular healing after hip arthroscopy.

Research objectives

To determine whether capsular repair or not may result in a capsular defect measured on an MRI scan. Secondary objective is to determine of the presence of a capsular defect might influence the clinical outcome after hip arthroscopy.

Research methods

A random sample of patients were enrolled in this case series. All were operated and had a magnetic

resonance imaging (MRI) scan in the postoperative phase. Patients were part of an earlier performed randomized trial and were randomized into a capsular repair or unrepaired capsulotomy group. Outcome was the presence of a capsular defect on MRI and the Copenhagen Hip and Groin Outcome Score (HAGOS).

Research results

A total of 29 hips were included. There was no significant different number of capsular defects between the capsular repair or unrepaired capsulotomy groups. There was also no difference in outcome measured with HAGOS outcome score between the capsular defect or capsule intact group.

Research conclusions

There was no difference in the number of capsular defects between the capsular repair or unrepaired capsulotomy group.

Research perspectives

Future larger studies are needed to confirm that capsular repair or unrepaired capsulotomy has no influence on the presence of a capsular defect or not. In addition; long term analysis needs to be done to determine whether the presence of a capsular defect might result in long term complications or influence outcome.

FOOTNOTES

Author contributions: Bech NH drafted the manuscript, was involved with data collection, and assisted with data analysis; van Dijk LA drafted the manuscript and participated in design of the study; de Waard S was involved with data collection, and assisted with data analysis; Vuurberg G drafted the manuscript, and assisted with data analysis; Sierevelt IN participated in study design and performed statistical analysis; Kerkhoffs GM participated in study design; Haverkamp D participated in design of the study drafted the manuscript and was involved with data collection; and all authors read and approved the final manuscript.

Institutional review board statement: This study was part of an earlier performed randomized controlled trial. This trial was approved by the local medical ethical committee and was registered at the CCMO Dutch Trial Register: NL55669.048.15.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors declare that there is no conflict of interest.

Data sharing statement: No additional data are available.

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LETTER TO THE EDITOR

Existing fixation modalities for Jones type fifth metatarsal fracture fixation pose high rates of complications and nonunion

Albert Thomas Anastasio, Selene G Parekh

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Abstract

Jones type fifth metatarsal fractures pose a challenge to the foot and ankle surgeon, given documented high nonunion rates as well as high complication rates including hardware prominence, nerve injury, and screw breakage for existing treatment modalities including screw and plantar plate fixation. We call for the design of innovative Jones-fracture specific implants which contour to the natural curve of the fifth metatarsal. Future research should aim to expand upon existing literature for Jones fracture fixation and evaluate efficacy of novel implants which are designed to address unacceptably high complication rates for existing treatment modalities.

Key Words: Jones; Metatarsal base; Fifth metatarsal; Athlete; Nonunion; Malunion

Core Tip: Jones type fifth metatarsal fractures have high rates of complications and fixation failure. While intramedullary screw fixation is the current accepted treatment modality, we call for innovation in the treatment options for Jones fracture fixation to more appropriately address the challenges seen with this fracture pattern in the high level athlete.

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TO THE EDITOR

We read with interest a review article from Albloushi *et al*[1], who present an excellent overview of pathoanatomy, classification, and current concepts of fixation modalities for Jones type fifth metatarsal fracture. We thank the authors for this valuable contribution, and we agree with their conclusion that there remains a lack of consensus on the effective management of Jones fractures, especially in the high-level athlete group. In part, we believe this lack of consensus may be due to unacceptably high complication rates of existing surgical treatments.

Both delayed union and nonunion remain a challenging problem after Jones fracture fixation. The authors note that delayed union in zone 2 and 3 fractures are often the result of choosing screws that are smaller than 4.5 mm in diameter. They recommend utilization of larger screw diameters, especially in the athlete population. While we agree that smaller diameter screws often contribute to nonunion after Jones fixation, we also draw attention to the risk of cortical perforation and subsequent impingement related symptoms, and even potential nerve injury with use of the larger diameter screws[2]. The authors also mention the challenge in adequately appreciating the natural curvature of the fifth metatarsal during fracture fixation. The authors note that failure to maintain the screw within the cortical bone of the 5th metatarsal remains a major cause of nerve injury[3], and recommend meticulous choice of proper entry point of the guidewire and screw with the correct trajectory within the medullary canal. Still, achieving proper positioning of a straight screw within a bone with natural curvature is difficult, and the challenge is expounded when attempting to utilize a larger diameter screw in the case of the elite athlete. Moreover, cannulated screws have been shown to lack proper strength to withstand the significant and repetitive forces the fifth metatarsal must sustain and have been shown to be associated with screw breakage[4].

Despite the difficulties encountered with screw fixation of Jones fracture, plate fixation is also associated with substantial complication risk[5]. Nonunion rates have been unacceptably high in some series[6], and calcaneus autograft has become commonplace for the procedure, denoting an additional area of potential patient morbidity[7]. Hardware prominence also presents a unique challenge in the plating of the Jones fracture. Furthermore, soft tissue injury with the dissection required for proper plate placement flush against the cortical bone can be associated with nerve injury and periosteal stripping with destruction of native bone biology potentially impeding bony union.

With the high complication rates associated with the existing fixation modalities (intramedullary screw fixation and plantar plate fixation), there remains area for innovation with regards to treatment modalities for Jones fracture. Our institution has begun use of an intramedullary implant created specifically for Jones fracture fixation which we hope will be effective in reducing some of the listed complications. This implant has an inherent curve which is fabricated to closely aligned to the natural curvature of the fifth metatarsal. Furthermore, the implant has an end cap which serves to both compress across the fracture site and to reduce hardware prominence at the insertion site. To further enhance fixation at the distal end of the metatarsal, the implant has a talon based mechanism which once activated, provides further implant purchase distally to prevent screw pullout. A study at our institution is currently underway to evaluate whether or not these features lead to decreased complication rates and increased return to play and decreased time to bony union after Jones fracture fixation.

In summary, Jones fracture fixation remains a challenging problem for the foot and ankle surgeon. Existing treatment modalities are associated with high complication rates. Future research should aim to improve upon design elements of existing implants in an effort to effectively manage patients with this condition.

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FOOTNOTES

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