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Research Article

Aspartate aminotransferase (AST) is not a viable biomarker for skeletal muscle damage. An enquiry during a total hip replacement randomized study

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Abstract. Introduction. Muscle damage can be caused by traumatic or metabolic injuries. In either case, damage to the muscle cells leads to expulsion of the intracellular content. This was a propellant to evaluate muscle damage caused by surgical trauma using an intracellular marker as aspartate aminotransferase (AST) during cement-less total hip arthroplasty. Objectives. The main objective of this study was to evaluate the differences in muscle damage between the muscle sparing direct anterior approach (DAA), and the trans-gluteal lateral approach (LA) by dynamically assessing levels of aspartate aminotransferase (AST) and comparing the results with a higher sensibility marker as myoglobin. Material and Method. One hundred and two (102) patients were randomized into two equal groups. Baseline values of AST where taken, but also of myoglobin for referencing. Patients underwent a total hip arthroplasty either through the DAA or LA according to the randomization protocol. AST levels where checked daily for the first 5 postoperative days, whilst myoglobin was evaluated 6 hours postoperatively. Results. There was clinically and statistically significant more muscle damage in the LA group according to myoglobin levels. There were higher levels of AST in postoperative day 2 in the LA group relative to the DAA group. AST has also significantly increased from base values in LA group in day 2 and 3 relative to the DAA group. When comparing preoperative AST levels to postoperative levels there were no clinically significant difference in any of the groups, in any days. AST did not reach in median pathological levels, regardless of time or approach. Conclusion There is less muscle damage through the DAA confirmed by myoglobin levels compared to the lateral approach when performing a total hip replacement, but AST is not sensitive enough to detect clinically significant variations.

Key Words: direct anterior approach, total hip arthroplasty, myoglobin, aspartate aminotransferase (AST), muscle damage biomarker.

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Introduction

Total hip arthroplasty (THA) is one of the most frequent surgical procedure done worldwide, and in the same time the most successful (Knight et al 2011, Chechik et al 2013). When performing a THA, the main objectives should be increasing patient's quality of life by relieving pain and restore functionality, implanting a long-lasting carefree endoprosthesis, through a painless procedure, followed by a rapid recovery without complications. With these high expectations from patients and surgeons alike, there are numerous variations to the procedure. Surgical approach and prosthesis design and fixation are the most influential in the outcome, with continuous evolution and progress (Chechik et al 2013).

The surgical approach has a potential influence on postoperative pain levels and rehabilitation protocols, while prosthesis design and fixation more on the hip system's overall life span. The main differences between approaches are muscle dissection and ease of exposure and access to the hip join.

Most used approaches worldwide (Chechik et al 2013) are the lateral approach (42%), posterior approach (45%) and direct anterior approach (10%). Out of this three, only the direct anterior approach (DAA) promises to be a completely muscle sparing technique, access to the hip joint being realized by intermuscular and interneurons planes.

Routinely used biomarkers of muscle damage are intracellular enzymes or proteins that show the functional status of muscle tissue. Surgical damage to the muscle cell can lead to expulsion of the intracellular content into the bloodstream (Huang et al 2006). Serum markers specific to direct tissue damage are creatine kinase (CK), lactate dehydrogenase (LDH), aldolase, aspartate aminotransferase, troponin and myoglobin (Brancaccio et al 2010). While LDH, CK and myoglobin were used previously to determine differences in muscle trauma between the two approaches (Nistor et al 2017), AST is another intracellular

marker considered for quantifying muscle damage (Brancaccio et al 2010).

AST, also known as glutamic oxaloacetic transaminase, found in the cell's cytoplasm and mitochondria is specific to the heart muscle, skeletal muscle, liver and many other, in contrast to alanine aminotransferase(ALT) which is more specific primarily to the liver (Gowda et al 2009). Because there is such a strong association of AST and ALT with liver pathology within the physician's diagnostical pathway, that serum elevation is rarely attributed to muscle or heart damage. However, it is known there are isoenzymes in skeletal muscles including AST, ALT, CK, LDH that are released into the bloodstream after muscle damage (Nathwani et al 2004).

Although there are previous studies evaluating AST as a biomarker for muscle damage after prolonged exercise, muscular dystrophy and rhabdomyolysis (Lippi et al 2008, Smith et al 2004, Kohli et al 2005), we had the opportunity to evaluate the fluctuation in a surgically controlled muscle dissection environment. The main purpose of this study was to evaluate the dynamic changes in postoperative AST levels after a muscle sparing hip replacing surgery like the DAA and after a more traumatic gluteus medius and vastus lateralis dissecting THA, as the LA.

Materials and methods

All patients enrolled were hospitalized between March 2015 and November 2018 in Emergency University County Hospital, Department of orthopedics and traumatology, Cluj-Napoca. This study was approved by the local Institutional Review Board – (IRB reference nr. 517/2015) and registered to clicnicaltrials.gov (NCT02719236). We established our inclusion criteria for this study as patients between 35 and 80 years of age, that were diagnosed with hip degenerative arthritis in need of surgical treatment (i.e. total hip replacement). The exclusion criteria considered was any history of chronic liver disease or acute heart or skeletal muscle pathology, patients that did not have a normal preoperative liver function test that included albumin, total protein, AST, alanine transaminase, gamma- glutamyl transferase, bilirubin, lactate dehydrogenase and prothrombin time. Patients that had pathologically high preoperative myoglobin levels were also excluded from this study. Other exclusion criteria were patients in need of any other type of prosthesis but a cement less one, and patients with any other diagnosis, especially traumatic patients, in need of a hip replacing procedure. We enrolled patients in this study after signing a written informed consent. We then conducted a computer-generated randomization to assign patients into one of the two groups, depending on the approach to be used (i.e. DAA group and LA group). The laboratory technicians were oblivious of the approach used in each case. By this means we tried to maintain an investigative blind status for the study.

Age, gender, height, weight and BMI were noted for each patient to compare demographics between groups.

All patients were operated under spinal anesthesia, by the same surgical team. Cement-less hip systems were used in all cases: Zimmer Biomet® Metabloc™ stems with Trilogy acetabular systems (Zimmer Warsaw, IN, USA) and DePuy-Synthes Corail® stems and Pinnacle® acetabular systems (DePuy Synthes ©. USA). Postoperative protocols were the same in both groups.

Patients in the DAA group underwent the total hip replacing surgery through the modified Smith-Peterson approach (Hueter 1883, Lovell 2008, Nistor et al 2018). This approach is considered as muscle sparing as it is carried out through intermuscular planes, without any muscle dissection. With the patient supine on the operating table, an eight cm incision is made starting two finger withs distally and laterally to the anterior superior iliac crest. The incision is made over the tensor fascia lata muscle (TFL). Then the fascia of the TFL is incised and the muscle retracted laterally, thus exposing the Hueter interval. After cauterizing the anterior circumflex vessels, an anterior capsulectomy was performed and joint exposure was reached. After performing a neck osteotomy and extracting the femoral head, acetabular and femur preparation were then carried out. A cement-less prosthesis was press fitted in place. Wound closure was done with resorbable sutures after a surgical drainage system was put in place.

Patients in the LA group were operated using the standard transgluteal Hardinge approach (Hardinge 1982). With the patient in the same supine position, an 8-10 cm incision was done over the grater trochanter. The underling subcutaneous and fascia lata were split in order to reach the vastus lateralis and gluteus medius muscles that were dissected. An antero-lateral capsulectomy was then performed and the joint was breached. After the femoral head and neck were extracted, acetabular and femur preparation was carried out. The same cementless hip system was used as previously.

Muscle damage was evaluated using biomarkers for muscle damage. Serum AST and myoglobin levels were collected in the morning (07:30 AM) prior to surgery to establish their base values. AST was measured daily for the first 5 postoperative days, in the morning, at 07:30 AM, and myoglobin 6 hours after surgery. Troponin levels were also acquired concomitant with myoglobin (i.e. preoperative and 6 hours postoperative), but due to the lack of needed laboratory reagents, we had to analyze the serum abroad. This led to a procedural error during transportation that meant the laboratory results could not be reliable.

Normal range values from our laboratory for AST is 5-50 U/L. Normal myoglobin values are less than 80 ng/mL.

After reaching 102 patients we have done a post hoc power analysis using G*Power 3.1.9.4 (Faul et al 2007). Establishing the main result as difference in muscle damage evaluated through the more specific marker as myoglobin, we applied a t test – for difference between preoperative and postoperative levels from the two groups. With a determined effect size of 1.360; p set at 0.05 and equal group sample size of 51, we obtained a study power of 99.99%.

Shapiro – Wilk normality test was applied for all variables. Normally distributed variables were assessed using the Student's t test and presented as mean ± standard deviation; non normally distributed variables were compared with the Mann – Whitney test, and presented as median (first quartile, third quartile). Categorical variables are described as percentage and frequency, whilst the difference between them were assessed using Fisher's exact test or Chi-square test. Difference between measurements were tested using the two-way ANOVA for repeated measurements, after the values were log-transformed. Alpha error probability was established at $p<0.05$. Statistical analysis was done using R version 3.1.1(R Core Team, Vienna, Austria).

Results

There was no difference in demographics between groups regarding age, weight, height and BMI, although we did see a difference in gender distribution. There were more female patients in the DAA group – 36 (70.6%) compared to the lateral group – 24 (47.1%), p=0.015.

Median age in LA group is 64(56;68), and 65(52;71) in the DAA group, p=0.643. Mean BMI in the DAA group is 27.45± 2.84 and in the LA group 28.43±2.95, with no significant difference between the two groups(p=1.95).

Preoperative and postoperative levels of myoglobin and AST are shown in Table 1 (Table 1). Preoperative levels of AST and myoglobin did not differ between groups. Postoperative myoglobin levels were highly statistically significant higher in the LA group (p<0.001). Although AST levels were more elevated post-surgery in the 1st, 2nd, and 3rd day in the LA group, and higher in the 4th and 5th day in DAA group, there was no statistically significant difference (Table 1, Fig. 1).

Table 1: Preoperative and postoperative aspartate aminotransferase (AST) and myoglobin levels after total hip replacing surgery

Variable	DAA group (n=51)	LA group (n=51)	p
Myoglobin preoperative	30.2(27.1;32.1)	30.9(25.9;36.1)	
Myoglobin 6 h postoperative	223(209;286)	324(276;381)	<0.001
AST preoperative	20(17;21)	16(15;23)	0.2
AST postoperative day 1	23(18;28)	23(20;32)	0.5
AST postoperative day 2	22(17;33)	29(20;33)	0.1
AST postoperative day 3	25(19;35)	25(22;40)	0.5
AST postoperative day 4	32(22;46)	28(24;35)	0.2
AST postoperative day 5	32(22;42)	28(22;34)	0.1

DAA = direct anterior approach, LA= lateral approach, AST = aspartate aminotransferase; AST measured in U/L; Myoglobin measured in ng/mL; median (first quartile; third quartile); Mann-Whitney test for all variables

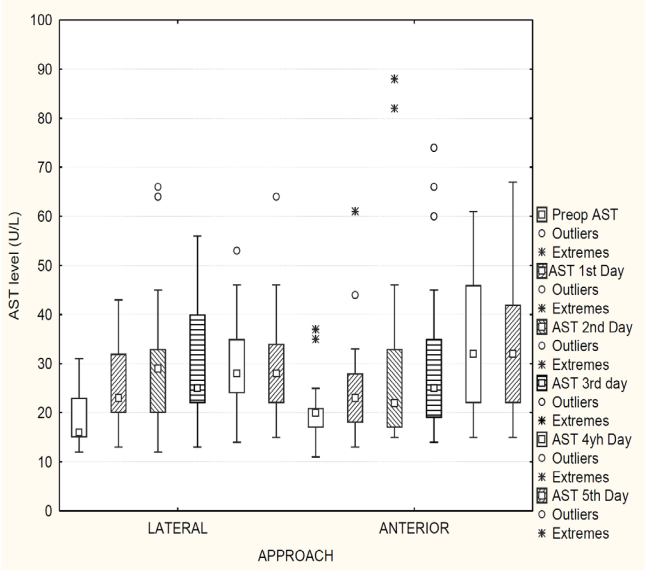

Figure 1. AST dynamic variation from preoperative to postoperative day 5 after total hip arthroplasty through the lateral approach (LATERAL), and direct anterior approach (ANTERIOR)

Discussions

As proven before (Nistor et al 2017), myoglobin levels are significantly higher in the LA group then the DAA group, showing as expected less muscle damage with the muscle sparing DAA, rather than with the trans gluteal lateral approach. We registered also an increase in myoglobin levels of seven fold in the DAA group and tenfold in the LA group, relative to preoperative results, showing not only that myoglobin is sensible to detect muscle damage caused by surgical trauma, but that there is muscle tissue affected also in the muscle sparing anterior approach. Confirming these results are other studies (Pilot et al 2006) but also intraoperative findings. With the LA, there is by nature muscle damage, as access to the hip joint is done through the vastus lateralis and gluteus medius muscles, explaining the increase of more than 10 times the normal values. The increase in myoglobin levels in the DAA group is at first somewhat unjustified, but during the procedure, the joint muscles – TFL, rectus femoris and sartorius are retracted out of the way to ensure access to the joint. During this maneuver, the muscles are elongated, compressed and sometimes even fibrous tears and blunt trauma can occur, especially in the TFL muscle. Normal AST levels in serum do not surpass 40 U/L, but when an organ such as the liver or the heart is damaged, this level rises 10 to 20 times than normal (Huang et al 2006). Although skeletal muscle is the third most frequent place that the enzyme AST is to be found, we did not register any significant modifications in serum concentration after neither of the approaches. Results from the AST enquiry were expected to resemble those of the myoglobin findings, although not the case. AST levels did increase in median in all postoperative days relative to base values, but it was not statistically or clinically relevant. Postoperative levels were expected to rise within the first 5 days, and reach high values at least in the LA group, where muscle damage is confirmed. Although the reference biomarker – myoglobin levels did statistically and clinically increase after total hip replacing surgery, AST levels remained in median within physiological limits.

Similar dynamics of AST were seen in a study evaluating biomarkers after physical exercise (Pettersson et al 2007). Levels started to rise in the first day after the exercise, peaking in the 4th, and gradually decreasing afterwards. All subjects in their study had values above the upper reference in the 3rd, 4th and 5th day. We had the same dynamics in both the DAA group and the LA group, but none of the median values surpassed the upper limit in a clinically significant matter.

A study evaluating half marathon runners (Lippi et al 2008) have seen similar results as ours, with AST levels increasing within the first 24 hours, but not surpassing physiologic limits, while myoglobin levels rose significantly over the reference range within the first 3 to 6 hours, showing again the clinical importance of myoglobin, and also the lack of sensibility for AST when assessing muscle damage.

Previous studies (Peterson et al 2007; Lippi et al 2008), evaluating skeletal muscle damage during muscular exercise by evaluating liver markers as AT, ALT, bilirubin, but also CK, LDH and myoglobin have shown that liver function test are increased after fiscal strain, although some (Akmal et al 1990) have shown the reason to be a form of reversible hepatic dysfunction rather than muscle damage.

Our study has some limitations. Given that all surgeries were done under spinal anesthesia, with analgesia and intravenous (i.v.) perfusion at the anesthesiologist's discretion, we are not able to determine their effect on AST levels and liver functionality, as well as blood dilution. Postoperative protocols for analgesia and i.v. intake was standardized in all patients and adjusted for theirs weight. Another limitation is not recording ALT levels, as the ratio AST/ALT can steer the physician to determine the probable cause, although this proved not to be an issue as AST levels did not reach pathologic status.

Conclusion

There is less muscle damage through the DAA confirmed by myoglobin levels compared to the lateral approach when performing a total hip replacement, but AST is not sensitive enough to detect any clinically significant variations regardless of the approach or postoperative elapsed time.

References

Akmal M, Massry SG, Reversible Hepatic Dysfunction Associated with Rhabdomyolysis. American Journal of Nephrology 1990;10(1):49–52.

Brismar BH, Hallert O, Tedhamre A, Lindgren JU, Early gain in pain reduction and hip function, but more complications following the direct anterior minimally invasive approach for total hip arthroplasty: a randomized trial of 100 patients with 5 years of follow up. Acta Orthopaedica 2018;89(5):484–9.

Chechik O, Khashan M, Lador R, Salai M, Amar E, Surgical approach and prosthesis fixation in hip arthroplasty world wide. Archives of Orthopaedic and Trauma Surgery 2013;133(11):1595–600.

Faul F, Erdfelder E, Lang AG, Buchner A, G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods 2007;39:175-191.

Gowda S, Desai PB, Hull VV, Math AA, Vernekar SN, Kulkarni SS, A review on laboratory liver function tests. Pan Afr Med J. 2009;22;3:17. PMID: 21532726; PMCID: PMC2984286.

Hardinge K, The direct lateral approach to the hip. J BoneJointSurg. 1982;(Br) 64:17–19.

Hueter C, Fünfteabtheilung: die verletzung und krankheiten des hüftgelenkes, neunundzwanzigstescapitel. In Hueter C. (eds): Grundriss der chirurgie, 2nd edition. Leipzig 1883;FCW Vogel, pp. 129-200.

Huang XJ, Choi YK, Im HS, Yarimaga O, Yoon E, Kim HS, Aspartate Aminotransferase (AST/GOT) and Alanine Aminotransferase (ALT/GPT) Detection Techniques. Sensors 2006;6(7):756–782.

Knight SR, Aujla R, Biswas SP, Total Hip Arthroplasty – over 100 years of operative history. Orthopedic Reviews 2011;3(2):16.

Kohli R, Harris DC, Whitington PF, Relative Elevations of Serum Alanine and Aspartate Aminotransferase in Muscular Dystrophy. Journal of Pediatric Gastroenterology and Nutrition 2005;41(1), 121–124.

Lippi G, Schena F, Salvagno GL, Montagnana M, Gelati M, Tarperi C, et al. Acute variation of biochemical markers of muscle damage following a 21-km, half-marathon run. Scandinavian Journal of Clinical and Laboratory Investigation 2008;68(7), 667–672.

Lovell TP, Single-incision direct anterior approach for total hip arthroplasty using a standard operating table. J Arthroplast 2008;23(7):64–68.

Nathwani RA, Pais S, Reynolds TB, Kaplowitz N, Serum alanine aminotransferase in skeletal muscle diseases. Hepatology 2005;41(2), 380–382.

Nistor DV, Caterev S, Bota NC, Lucaciu D, Todor A, Total hip arthroplasty via the direct anterior approach versus lateral approach: study protocol for a randomized controlled trial. Clinical Trials in Orthopedic Disorders 2018;3:18. Nistor DV, Caterev S, Bolboacă SD, Cosma D, Lucaciu DOG, Todor A, Transitioning to the direct anterior approach in total hip arthroplasty. Is it a true muscle sparing approach when performed by a low volume hip replacement surgeon? International Orthopaedics 2017;41(11), 2245–2252.

Pettersson J, Hindorf U, Persson P, Bengtsson T, Malmqvist U, Werkström V, Ekelund M, Muscular exercise can cause highly pathological liver function tests in healthy men. British Journal of Clinical Pharmacology 2008; 65(2), 253–259.

Pilot P, Kerens B, Draijer WF, Kort NP, Kate J, Buurman WA, Kuipers H, Is minimally invasive surgery less invasive in total hip replacement? A pilot study. Injury 2006;37, S17–S23. doi:10.1016/s0020-1383(07)70007-4.

Smith JE, Effects of prolonged strenuous exercise (marathon running) on biochemical and haematological markers used in the investigation of patients in the emergency department. British Journal of Sports Medicine 2004; 38(3), 292–294. doi:10.1136/bjsm.2002.002873.

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