Splint Duration and Not the Mode of Anesthesia Is the Main Factor Influencing Avascular Necrosis After Closed Reduction for Developmental Dysplasia of the Hip in Kosovo

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The aim of this study was to determine whether the use of analgesia and sedation (AS) as opposed to general anesthesia (GA) for closed reduction and spica casting of children with severe developmental dysplasia of the hip (DDH) influenced the long-term incidence of avascular necrosis (AVN). In a prospective, randomized, single-blinded clinical trial we investigated 100 pediatric patients with DDH type IIIa, IIIb, and IV (according to Graf classification), who were randomly assigned into the group receiving AS, and the group receiving GA. Baseline demographics, splint duration, and type of DDH were carefully assessed. The presence of AVN was assessed at the follow-up visits at 1 and 7 years after the end of treatment. The AS-group consisted of 50 patients (46 girls) with 76 hips affected (n = 11/Type-IIIa, n = 32/Type-IIIb, and n = 33/Type-IV). The GA-group consisted also of 50 patients (44 girls) with 78 hips involved (n = 15/Type-IIIa, n = 34/Type-IIIb, and n = 29/Type-IV). At 7-years follow-up, AVN was diagnosed in 9 of 154 hips (5.8%), 5 hips in the AS-group and 4 hips in the GA group. The logistic regression model showed no significant difference in AVN incidence between the AS and GA groups at 7-years follow-up (p = 0.27). The multivariate regression analysis showed that neither the type of DDH nor the age at diagnosis influenced the incidence of AVN (p = 0.48 and p = 0.28, respectively). Splint duration was identified as the only significant factor for the long-term incidence of AVN in the treatment of severe DDH. For every month of longer splint duration, the odds of AVN at 7-years follow-up increased by a factor of 3.81 (95% CI: 1.35–13.73, p = 0.02). Closed reduction and spica casting of children with severe DDH under AS can be considered a feasible alternative to management under GA. All efforts must be made to diagnose patients with DDH as early as possible and shorten the duration of splint treatment to prevent the development of AVN. Level of Evidence. Level II-1.

Keywords: developmental dysplasia of the hip, analgesia and sedation, general anesthesia, splint duration, closed reduction
INTRODUCTION

Developmental dysplasia of the hips (DDH) remains a prominent pathology among children in Kosovo (1). Amid 31,002 live births in our country from 2011 to 2012, the overall rate of those presented with hip dislocation was 0.25% (2). During this period, the reported incidence rate of newborns treated with closed reduction (percutaneous traction, spica casting in human position, and dynamic splinting with Tübingen hip–flexion orthosis) was 0.18%, and the rate of cases treated with surgery was 0.07%. The closed reduction and spica casting are commonly performed procedures in our department to obtain concentric hip reduction and allow for acetabular and femoral remodeling with the lowest avascular necrosis (AVN) rate (3, 4). Bracing and splinting are shown to be the first line of DDH management with a low rate of AVN reported (5, 6).

Graf’s classification of hip dysplasia by ultrasound is a valuable tool for early recognition of all degrees of DDH, but due to lack of appropriate infrastructure, despite high incidence rate of DDH in our country, unfortunately, Kosovo still does not have a national screening program for DDH.

The incidence rate of AVN after closed reduction management of DDH ranges between 4 and 60% (3, 7). The main cause of AVN after closed reduction is iatrogenic and the main risk for developing AVN is late presenting children regardless of hip dysplasia classification (1). Previous reports have shown that early diagnosis of DDH, preliminary traction, gentle reduction under the use of general anesthesia (GA), adductor tenotomy, and avoidance of an extreme position of immobilization have helped decrease the incidence of AVN (3, 4, 7–10).

Although GA has been reported to be among the protective factors against the development of AVN (7, 8, 11, 12) in our institution closed reduction and spica casting was traditionally performed under analgesia and sedation (AS) due to limited resources in the operating theater. So far, the relationship between the type of used anesthesia and AVN is not yet explored.

The purpose of this study was to investigate whether there was any difference on the long-term AVN incidence depending on the type of anesthesia used during closed reduction treatment of DDH. We hypothesized that the incidence of AVN will be lower in children treated under GA as compared to those treated under AS.

MATERIALS AND METHODS

Study Design

The study is a prospective, randomized, single-blinded clinical trial with an 8-years assessment period and two-point in time follow-up visits. The first follow-up assessment is done in all trial patients 1 year after the end of the treatment. Only patients diagnosed with AVN during the first visit were subjected to a second follow-up assessment 7 years after the end of treatment. The interventional part of the study was conducted from January 2011 through October 2012. Final follow-up visits were conducted from June 2019 to December 2020.

The primary objective was to investigate whether the use of AS or GA during closed reduction management of DDH has any significant effect on subsequent AVN development. The secondary objectives were to investigate the role of patients’ age at diagnosis, gender, the number of affected hips, the affected side (right/left), the degree of initial hip dysplasia, and the duration of splinting on AVN development afterward. The only difference in the course of the treatment of these patients was the mode of anesthesia for closed reduction.

Online randomization1 for 200 patients was used to generate the randomization plan for two groups in a block of two patients to control for equal numbers between the groups. Subject recruitment was terminated after 100 patients were included in the trial.

The trial protocol was approved by the University Ethical Committee for Medical and Health Research of our country with approval number 02-2010. Signed and dated written informed consent of the parent (or the person having parental authority in the family) is obtained according to the 1964 Declaration of Helsinki.

At our institution, the standard treatment for children diagnosed with DDH type IIIa/IIIb/IV consists of inpatient percutaneous Bryan’s traction with approximately 10% of child body weight as weighted traction for 2 weeks, followed by closed reduction with arthrography, adductor tenotomy when a narrow safe zone is presented, and spica casting in human position (90–100 degrees flexion and 45–60 degrees abduction) for a period of 4 weeks (Figure 1). None of the patients wear

1http://www.graphpad.com/quickcalcs/index.cfm

FIGURE 1 | A 4.5-months-old baby-girl with left hip dislocation after closed reduction and spica casting.
Tübingen splint before casting. Further treatment is continued in the outpatient setting. Tübingen hip–flexion orthosis is used after removing the cast until we consider that the femoral head position is normal and stable throughout the ultrasound examination (13). Tübingen splint is removed only during clinical and US examination. We use Tübingen splint for every patient independently from age and body weight. Clinical and ultrasound checkups were conducted at intervals of 4 weeks. After 6 months of age, X-ray checkups were necessary.

**Study Population**

All consecutive patients diagnosed with DDH type IIIa/IIIb/IV (according to Graf’s classification) (14), during the study period were initially randomized into the study. Only patients with successful closed reduction and successful transition from spica casting to Tübingen splint were included into the study. Exclusion from the study followed 42 patients with 70 abnormal hips (28 bilateral, 8 left and 6 right) who all needed surgical intervention by Salter’s and/or Pemberton’s osteotomies combined or not with femoral osteotomies (15). Teratologic hip dislocation is seen in two of the patients, 2 patients failed closed reduction in both groups by one, and 38 patients were considered neglected cases, which means they were not diagnosed before walking age. After these exclusions, 100 patients (90 girls and 10 boys) with 154 dislocated hips (54 bilateral, 28 left, and 18 right) were included in the present study. Figure 2 describes the sample selection. Percutaneous adductor muscle tenotomy was performed in 12 patients, 5 in the AS group, and 7 in the GA group.

Perioperative management of all the patients consisted of administering midazolam 0.5 mg/kg BW orally with apple juice and paracetamol 15 mg/kg BW supp. rectally 30 min before the intervention, followed by transportation of the patients into the operation theater in their beds with legs under traction.

Patients were randomly allocated into two parallel groups: the AS group initially received iv fentanyl 1 mcg/kg BW and subsequently 1 mcg/kg as required (16, 17). The GA group received fentanyl 2–6 mcg/kg BW iv and later a maintenance dose of 0.5–2 mcg/kg BW (18). In addition, a bolus dose of iv propofol 2–3 mg/kg BW was administered, and for maintenance of anesthesia, 5–15 mg/kg/hour. Finally, an inhalational induction dose of sevoflurane 5% and for maintenance 0.5–2% was given (19). Airway management was performed by Ambu mask in the AS group and by laryngeal mask in the GA group. Postoperative management consisted of analgesia with paracetamol given as suppository 15 mg/kg BW t.i.d (20). Patients were discharged home with a spica cast on the first post-intervention day after re-evaluation was done by the orthopedic surgeon and the anesthesiologist.

**Data Collection**

Collected data for every study subject consisted of baseline demographics, clinical, and imaging details, for each included hip from the time of initial consultation to the most recent follow-up. At the baseline visit, clinical examination and ultrasound (US) was performed by the orthopedic surgeon to establish a full spectrum of DDH severity according to Graf sub-types (14). In all children US is used for evaluation and clinical decision-making.
However, US is limited to being less accurate with continued growth and ossification of the femoral head in the older infant (21). To this extent, anteroposterior pelvic radiographs were used in addition to US for assessing hips of the patients older than 6 months for the position of the hip reduction, the possibility of failure of reduction, and the radiological parameters that indicate the development of the osteonecrosis of the femoral head (14, 22). The radiographs were evaluated by both, the radiologists and the orthopedic surgeons in charge of the patient.

The first follow-up examination was performed for all patients 1 year after the end of treatment. Patients diagnosed with AVN at the 1st follow-up visit were referred for a second re-evaluation and follow-up was 7 years after the end of treatment. Both assessments were made by anteroposterior pelvic radiographs. Every patient’s parents were reminded by phone call, specifically before the scheduled follow-up visit, to ensure full compliance. No patients were lost to follow-up.

The presence of AVN in the follow-up radiographic evaluation was assessed by the criteria of Bucholz and Ogden’s classification (22) (Figure 3). Still, for the purpose of this manuscript and for statistical analysis each hip was only classified and calculated as "1/YES" vs. "0/NO" for radiographic evidence of AVN.

**Statistical Analysis and Study Variables**

The exact Wilcoxon test was used to analyze the difference between the two clinical trial groups for continuous features. Logistic regression analysis was performed to find a relationship between the independent (predictor) and dependent (target) variables in the closed reduction of DDH. Our study’s outcomes (dependent variables) were the frequency of AVN 1 year and 7 years after the end of treatment. The investigated risk factors (independent variables) were the type of anesthesia used during closed reduction (AS vs. GA), the DDH stages IIIa/IIIb/IV (coded numerically as 1/2/3, respectively), the age at diagnosis in months, gender, the number of affected hips, the affected side (right/left), and splint duration in months. Univariate models were calculated separately for each risk factor. Multivariate models estimated a common linear predictor from the risk factors in the model. The dependence of splint duration from anesthesia, DDH stages, gender, the number of affected hips, the affected
side (right/left), and age at diagnosis was similarly investigated by linear regression analysis.

Statistical significance was set at a p-value <0.05. Categorical variables are reported as percentage and frequency. Continuous variables are presented as a measure of central tendency (mean or median) and spread (SD or range). Confidence intervals (CI) are calculated at the 95% level.

Statistical computing and graphics are performed using R 4.0.2 software.

RESULTS

Patient demographic data are described in Table 1. A total of 154 hips were treated in 100 children. There was no statistically significant difference in the incidence of bilateral DDH or the affected hip side between the groups. Also, there was no statistical difference in the type of DDH between the two study groups (p = 0.35, exact Wilcoxon test).

There was an overall strong female predominance (90%) without significant differences between the groups. Treatment was done in 138 hips in female patients and 16 hips in male patients.

The age at diagnosis ranged from 1.6 to 8.7 months, with a mean of 3.7 (± 1.4) months and a median of 3.3 months. Children in the GA group were significantly younger than children in the AS group (p = 0.016, exact Wilcoxon test).

Avascular necrosis was diagnosed in 15/154 hips (9.7%), 1 year after completing treatment. At 7 years follow-up AVN was still present in 9/15 hips (5.8%) (Figure 4 and Table 2).

The logistic regression model (Figures 4, 5) for AVN showed no significant difference in the development of AVN between AS and GA groups. Therefore, the mode of anesthesia did not affect the occurrence of AVN. Both the univariate and multivariate analyses revealed that the type (degree) of DDH was not a significant risk factor for AVN development, which was true for both follow-up periods.

The univariate logistic regression model identified age at diagnosis as a significant risk factor for AVN development (p < 0.001), for both follow-up periods (Figures 4, 5). However, with splint duration in the multivariate analysis, age at diagnosis became an insignificant factor (p = 0.1).

### Table 1 | Demographic characteristics of patients.

|                      | AS      | GA      | Total   |
|----------------------|---------|---------|---------|
| N of patients        | 50      | 50      | 100     |
| Age at diagnosis in months (median and range) | 3.6 (2.3–8.6) | 3.1 (1.6–8.7) | 3.3 (1.6–8.7) |
| Girls N (%)          | 46 (92%)| 44 (88%)| 90 (90%)|
| Boys N (%)           | 4 (8%)  | 6 (12%) | 10 (10%)|
| Bilateral DDH N (%)  | 26 (52%)| 28 (56%)| 54 (54%)|
| Unilateral DDH N (%) | 24 (48%)| 22 (44%)| 46 (46%)|
| Total number of hips with DDH | 76 | 78 | 154 |
| Left hip (N)         | 40      | 42      | 82      |
| Right hip (N)        | 36      | 36      | 72      |
| Type of DDH N (%)    |         |         |         |
| IIIa                 | 11 (15%)| 15 (19%)| 26 (17%)|
| IIIb                 | 32 (42%)| 34 (44%)| 66 (43%)|
| IV                   | 33 (43%)| 29 (37%)| 62 (40%)|

N, number; AS, analgesia and sedation; GA, general anesthesia; DDH, developmental dysplasia of the hip.

### Table 2 | Outcome characteristics of patients.

|                      | AS      | GA      | Total   |
|----------------------|---------|---------|---------|
| N of patients        | 50      | 50      | 100     |
| AVN at 1 year (N of patients) | 8 (16%) | 5 (10%) | 13 (13%) |
| AVN at 7 years (N of patients) | 4 (8%)  | 4 (8%)  | 8 (8%)  |
| N of hips in groups  | 76      | 78      | 154     |
| AVN at 1 year (N of hips) | 10 (13%)| 5 (6%)  | 15 (10%)|
| AVN at 7 years (N of hips) | 5 (7%)  | 4 (5%)  | 9 (6%)  |
| AVN Left hip at 1/7 years (N) | 5/2    | 1/1    | 6/3     |
| AVN Right hip at 1/7 years (N) | 5/3    | 4/3    | 9/3     |
| Type of DDH in AVN hips at 1/7 years (N) |         |         |         |
| IIIa                 | 3/1     | 1/1     | 4/2     |
| IIIb                 | 4/1     | 0/0     | 4/1     |
| IV                   | 3/3     | 4/3     | 7/6     |

N, number; AS, analgesia and sedation; GA, general anesthesia; AVN, avascular necrosis; DDH, developmental dysplasia of the hip.
Splint duration was identified as the only significant variable, which affected AVN at 7-years follow-up in multivariate analysis ($p = 0.02$). For every 4-week prolongation of splint duration, the risk of AVN at 1-year follow-up increased by a factor of 2.08 (95%CI: 1.34–3.34, $p < 0.002$) in univariate analysis and 1.41 (95%CI: 0.68–2.98, $p = 0.4$, not significant) in multivariate analysis (Figures 4, 5). For every 4-week of splint duration prolongation for the treatment of DDH, the odds of AVN at 7-years follow-up increased by a factor of 4.03 (95%CI: 2.13–9.13, $p < 0.001$) in univariate analysis, and 3.81 (95%CI: 1.35–13.73, $p = 0.02$) in multivariate analysis. AVN, avascular necrosis; AS, analgesia and sedation; GA, general anesthesia; N, number of affected hips.

The overall duration of splint treatment ranged from 2 to 7.2 months with a mean of 4.1 ($\pm$ 1.1) months and a median of 4.1 months. The results of univariate and multivariate linear regression analysis for splint duration are given in Figure 6. Splint duration was $-0.66$ months (95%CI: $-1.03$ to $-0.3$, $p < 0.001$) shorter in the GA group than in the AS group. The effect was $-0.39$ months (95%CI: $-0.63$ to $-0.15$, $p = 0.002$) after adjustment for independent variables in multivariate analysis. If the degree of dysplasia is higher by one stage, the splint duration is increased by 0.5 months in univariate analysis and 0.543 months in multivariate analysis ($p < 0.001$, respectively). For every month of age that the DDH treatment is delayed, splint duration is expected to increase by 0.54 months in both, univariate and multivariate analysis ($p < 0.001$, respectively). Finally, affection of both hips by DDH led to an increase of splint duration by 0.27 months (95%CI: 0.01–0.54, $p < 0.05$) in the multivariate analysis.

### DISCUSSION

The present study shows that closed reduction and spica casting under AS or GA in children with DDH leads to similar outcomes...
been defined by some authors as a risk factor for the development (1, 3, 4, 31). The splint duration over 4 weeks in older children has duration and AVN has been reported previously in the literature of AVN at 7-years follow-up. The relationship between splint up, i.e., the longer the splint duration, the higher the incidence significant influence on the incidence of AVN at 7-years follow-
up, i.e., the longer the splint duration, the chance to help the child to save the hip by open surgery might be missed (3, 4). Elseways, open reduction of DDH has been reported to be associated with twice as a higher risk of developing AVN of the femoral head as compared to closed reduction (3).

We examined the splint duration as a dependent variable by using the linear regression model. Splint duration lasted significantly longer in older children, in children with a higher degree of dysplasia, in children with both hips affected, and in children that were treated under AS. These variables seem to indirectly affect the incidence of AVN over prolonging splint duration.

Our study's limitation is that the randomization process did not consider the age of the included children. Unfortunately, the children randomized in the GA group were significantly younger than the children undergoing AS for closed reduction and spica casting. However, the logistic regression model corrects this difference. The older age of children at diagnosis and the degree of dysplasia remain high-risk factors for AVN development, although statistical significance was not reached in our study. Previous studies showed that AVN was more likely to occur in patients with a higher degree of initial dislocation and older age at diagnosis (7, 31). Furthermore, our findings could have been influenced by the initial management of our patients.

CONCLUSION

Closed reduction and spica casting of children with DDH under AS can be a feasible alternative to management under GA. All efforts must be put into early diagnosis of DDH and early treatment starting, as it reduces the need for long splint duration, which may be the leading risk factor for AVN development at 7-years follow-up. We believe that by introduction of a mandatory ultrasonographic screening program according to Graf’s classification, also in Kosovo, the incidence of high-degree DDH will decrease.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This interventional study was conducted at the Orthopedic Department of Kosovo University’s Clinical Center in Kosovo. The trial protocol was reviewed and approved by Kosovo’s University Ethical Committee for Medical and Health Research. Signed and dated written informed consent of the parent (or the person having parental authority in the family) is obtained according to the 1964 Declaration of Helsinki. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin.
AUTHOR CONTRIBUTIONS

SS and BB contributed in design, data acquisition, data analysis, data interpretation, and drafting of the manuscript. IK, AT, and AM contributed in data acquisition, and critical revision of the manuscript. FQ contributed in statistical processing of data and their interpretation. EH contributed in interpretation of data, drafting and critical revision of the manuscript. All authors provide final approval of the version to be submitted.

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