

BJO



## ■ CHILDREN'S ORTHOPAEDICS

# Day-case open reduction for developmental dysplasia of the hip

IS IT SAFE?

**M. Flatman,  
B. H. Barkham,  
E. Ben David,  
A. Yeo,  
J. Norman,  
Y. Gelfer**

From St George's  
Hospital, London, UK

## Aims

Open reduction in developmental dysplasia of the hip (DDH) is regularly performed despite screening programmes, due to failure of treatment or late presentation. A protocol for open reduction of DDH has been refined through collaboration between surgical, anaesthetic, and nursing teams to allow same day discharge. The objective of this study was to determine the safety and feasibility of performing open reduction of DDH as a day case.

## Methods

A prospectively collected departmental database was visited. All consecutive surgical cases of DDH between June 2015 and March 2020 were collected. Closed reductions, bilateral cases, cases requiring corrective osteotomy, and children with comorbidities were excluded. Data collected included demographics, safety outcome measures (blood loss, complications, readmission, reduction confirmation), and feasibility for discharge according to the Face Legs Activity Cry Consolidability (FLACC) pain scale. A satisfaction questionnaire was filled by the carers. Descriptive statistics were used for analysis.

## Results

Out of 168 consecutive DDH cases, 16 patients fit the inclusion criteria (age range 10 to 26 months, 13 female). Intraoperative blood loss ranged from "minimal" to 120 ml, and there were no complications or readmissions. The FLACC score was 0 for all patients. The carers satisfaction questionnaire expressed high satisfaction from the experience with adequate information and support provided.

## Conclusion

Open reduction in DDH, without corrective osteotomy, is safe and feasible to be managed as a day case procedure. It requires a clear treatment pathway, analgesia, sufficient counselling, and communication with carers. It is even more important during the COVID-19 pandemic when reduced length of hospital stay is likely to be safer for both patient and their parents.

**Cite this article:** *Bone Jt Open* 2021;2-4:271–277.

**Keywords:** DDH, Day-case, Open reduction

## Introduction

Developmental dysplasia of the hip (DDH) is the most common musculoskeletal condition in infancy. Screening programmes aiming to reduce late presentation differ around the world; from universal ultrasound screening, selective ultrasound screening, and universal radiographs at different ages.<sup>1,2</sup> In the UK, screening for DDH is undertaken according to the Newborn and Infant Physical Examination (NIPE) guidelines,<sup>3</sup> which recommend

clinical examination for every newborn and selective ultrasound screening based on clinical examination and risk factors.

Despite the screening programmes delayed presentations do occur and these children require surgical intervention. It is common practice in the UK to perform an open reduction of the hip for either late presentation or following a failed attempt of closed reduction.<sup>4</sup>

Correspondence should be sent to Yael Gelfer; email: yaelgelfer@gmail.com; yael.gelfer@stgeorges.nhs.uk

doi: 10.1302/2633-1462.24.BJO-2020-0199.R2

*Bone Jt Open* 2021;2-4:271–277.

| <i>Pre-operative counselling</i>   |
|--|
| <ul style="list-style-type: none"> <li>• Clinic appointment with the consultant responsible for their care.</li> <li>• Both consultants (**/**) used the same indications for open reduction</li> <li>• Extensive counselling regarding the nature of the operation and post-operative care as well as multiple sources of information provided including the STEPS leaflet and website as well as recommended social media support groups.</li> <li>• Information regarding car seats and push chairs as well as spica management was also provided.</li> <li>• Several families were seen more than once ahead of the procedure.</li> <li>• If English was not their first language an interpreter service was available</li> <li>• Presented to the paediatric surgical ward at 0730 on the morning of their procedure for last minute questions and final signing the consent form.</li> <li>• These cases were placed first on the operating list.</li> </ul> |
| <i>Anaesthesia</i>   |
| <ul style="list-style-type: none"> <li>• Consultant anaesthetist led care.</li> <li>• A combined general anaesthetic with a caudal epidural block.</li> <li>• Clonidine 2 microgram/kg added to the caudal block.</li> <li>• Antibiotic prophylaxis was administered intravenously (co-amoxiclav 30 mg/kg iv or cefuroxime 25 mg/kg if penicillin allergy) at induction of anaesthesia.</li> <li>• Intravenous paracetamol administered intraoperatively.</li> <li>• Analgesia was monitored and adapted at each step of the process.</li> </ul>   |
| <i>Surgery</i>   |
| <ul style="list-style-type: none"> <li>• Both consultant surgeons used the same modified Smith-Peterson approach with a 'bikini' incision for improved cosmesis.</li> <li>• The obstacles for reduction removed and capsulorrhaphy performed.</li> <li>• The 'test of stability' performed to aid in decision-making regarding need for an osteotomy.</li> <li>• Spica cast applied with extension to the ankle on the operated side and above the knee on the contralateral side. A broomstick augmentation was not used.</li> </ul>  |
| <i>Discharge</i>   |
| <ul style="list-style-type: none"> <li>• Post-operative consultant surgeon, consultant anaesthetist and ward nurse review to determine: <ul style="list-style-type: none"> <li>○ No significant blood loss or neurovascular compromise.</li> <li>○ No surgical or anaesthetic complications.</li> <li>○ Adequate analgesia determined using FLACC score.</li> <li>○ Thorough parental understanding of analgesia and spica cast care.</li> </ul> </li> <li>• Children were discharged when they had stable observations, could tolerate fluids, passed urine, and their pain was controlled.</li> <li>• The spica cast was reviewed by the consultant surgeon and the ward nurse before discharge.</li> <li>• All families given a point of contact in case they had any concerns.</li> </ul>  |
| <i>Aftercare</i>   |
| <ul style="list-style-type: none"> <li>• Five days of regular paracetamol and ibuprofen</li> <li>• As required dihydrocodeine and diazepam twice a day with dosages adjusted to age and weight.</li> <li>• Post-operative radiograph to confirm reduction</li> <li>• Outpatient clinic appointment within 14 days of the operation</li> <li>• The time in the spica cast is six weeks for the first period, a second examination under anaesthesia in theatre with another six weeks in a spica or brace (according to surgeon's preference).</li> <li>• Continued regular outpatient reviews as required.</li> </ul>  |

Fig. 1

St George's Hospital developmental dysplasia of the hip multidisciplinary protocol.<sup>13–15</sup> FLACC, Face Legs Activity Cry Consolidability.<sup>16</sup>

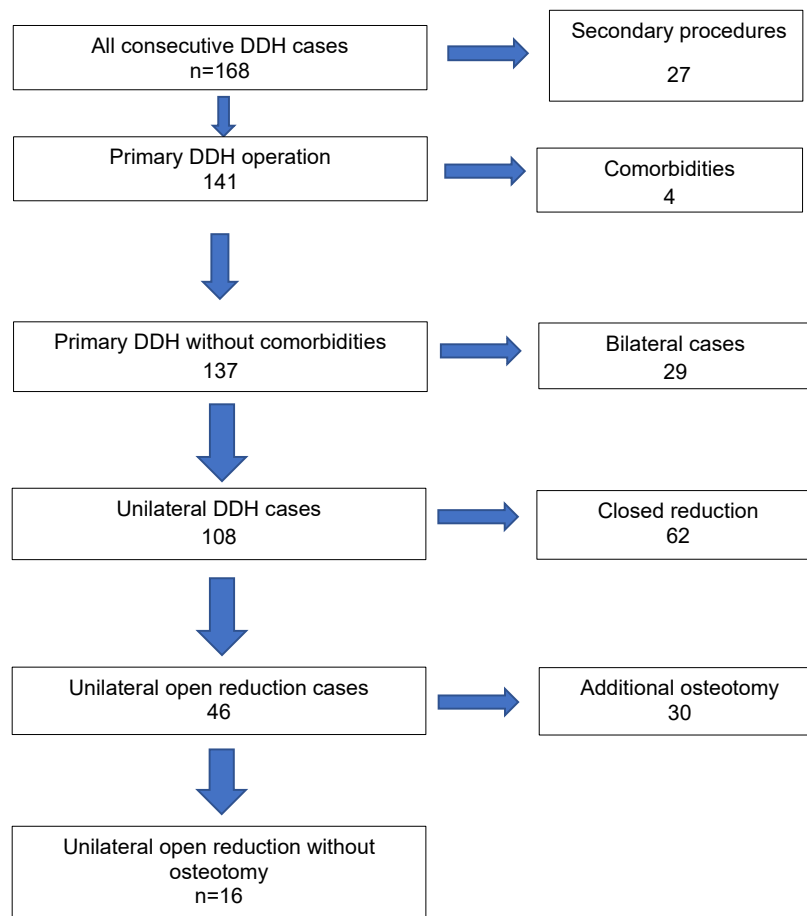


Fig. 2

Patient selection flow diagram. DDH, developmental dysplasia of the hip.

Healthcare providers are increasingly searching for ways to provide cost-efficient, high-quality care. The benefits of ambulatory orthopaedic surgery, especially in adult hip arthroplasty, have been shown to have both reduced costs<sup>5,6</sup> and increased satisfaction,<sup>7,8</sup> and comparable low rates of readmission compared to inpatient procedures.<sup>9</sup> In recent years the successful implementation of day case surgery has increased as both patient selection and perioperative care pathways have improved in both adults and children.<sup>10-12</sup>

Hospital stay for both closed and open reduction of DDH is determined according to the local hospital protocol in the absence of any specific national or international guidelines. Inpatient stay is normally prescribed for pain management, SPICA care training, or postoperative imaging. At our centre, closed reduction of DDH has been managed with same-day discharge since 2003 and open reductions with a one-night stay following the operation. Both surgical approaches and the perioperative anaesthetic protocols have improved, resulting in minimal blood loss and improved pain management.

Our centre has developed a multidisciplinary protocol allowing a same day discharge following hip open reduction (Figure 1).

The objective of this study was to evaluate the safety and feasibility of conducting open reduction of DDH as a day case. To our knowledge this is the first publication of this operation being done as a day case procedure.

## Methods

**Data collection.** Our prospectively collected departmental database was visited. All consecutive procedures for DDH between June 2015 and March 2020 were selected. These were filtered to exclude closed procedures, bilateral cases, and cases which required an osteotomy, as well as any children with comorbidities or neurodisability (Figure 2). A translation service was available for non-English speakers and no one was excluded based on this. The patients' electronic notes were interrogated. The following data were extracted: patient demographics, consultant surgeon, short-term outcome (determined by reduction confirmation on plain radiograph), blood

1. Did your child need pain relief overnight? Yes/No

1.1 If the answer is yes; did you know what to use? Yes/No

1.2 If the answer is yes; was it effective? Yes/No (A score of '1' if no pain or if pain was managed successfully, a score of 0 if the pain was not managed successfully)

2. Do you feel you received an adequate level of information to be able to control their pain at home after discharge? Yes/No (Yes=1, No=0)

3. Did you have a good experience on your first night following surgery? Yes/No (Yes=1, No=0)

4. Were you happy and comfortable, receiving adequate information and support, to take your child home on the night of the operation? Yes/No (Yes=1, No=0)

5. Have you received sufficient information regarding Spica management? Yes/No (Yes=1, No=0)

6. Were there any specific challenges you faced, other than pain management or Spica care, after discharge? Yes/No (No= 1, Yes=0)

6.1 If the answer is yes; could you specify the challenge.

\*A score of 6/6 was defined as feasible for same-day discharge

Fig. 3

Carers questionnaire.

loss, any surgical, anaesthetic, or other complication, and any case of readmission. The Face Legs Activity Cry Consolidability (FLACC) score<sup>16</sup> used for monitoring analgesia success was also collected from the notes.

A postoperative study-designed subjective satisfaction questionnaire was completed by the carers regarding their immediate postoperative experience (Figure 3). The design of this specific questionnaire for DDH aimed to seek a better understanding of the immediate postoperative experience related to this specific condition, and the potential obstacles and anxieties related to same day discharge. The questionnaire outcomes were pain management, spica cast management, adequate level of support, and information for the postoperative period. The completion of the questionnaire was conducted as a part of a routine clinical consultation by one of the junior doctors during the immediate postoperative period. The carers provided verbal consent for the questionnaire completion.

**Ethical approval.** Consultation with the Health Research Authority deemed this study a service evaluation project to determine safety and feasibility related to standard of care (Reference AUDI000386). Verbal consent was collected from parents before agreeing to answer the questions in the feasibility questionnaire in an anonymized format.

**The St George's Hospital approach.** Children with late presenting DDH or failed Pavlik Harness treatment are managed by closed reduction (with or without an adductor and iliopsoas tenotomy) or open reduction (with or without osteotomy). The end procedure was dependent on the patient's age and findings on evaluation under anaesthesia (EUA) and arthrogram. These procedures may be followed by a further EUA (with or without an arthrogram) to determine stability of the reduced hip. In cases of an unsuccessful closed reduction, a decision is made to proceed with an open reduction (with or without an osteotomy) at a later sitting. A protocol for open reduction of DDH has been refined through collaboration between surgical, anaesthetic, and nursing teams to allow same day discharge.

Patients and families were counselled in clinic prior to the surgery and all treatment options were explained in length. The families were expecting the final decision regarding the need for an osteotomy to be made in theatre, and were counselled to prepare for an admission in case of an added osteotomy and for a same day discharge in case of an open reduction without an osteotomy pending feasibility. The surgical technique was consistent and all procedures were performed by one of two senior authors (YG, AY).

| Question      | Yes                        | No       | Comments   |
|---------------|----------------------------|----------|--|
| 1             | 16 (100%)                  | x        |  |
| 1.1           | 16 (100%)                  | x        |  |
| 1.2           | 16 (100%)                  | x        |  |
| 2             | 16 (100%)                  | x        |  |
| 3             | 15 (94%)                   | 1 (6%)   | Patient was unwell. Later diagnosed as Chicken Pox |
| 4             | 15 (94%)                   | 1 (6%)   | Patient was unwell. Later diagnosed as Chicken Pox |
| 5             | 16 (100%)                  | x        |  |
| 6             | 1 (6%)                     | 15 (94%) |  |
| 6.1           | 1 (6%)                     | 15 (94%) | Needed more information re spica car-seat          |
| <b>Totals</b> | 15 Carers scored 6/6 (94%) |          | 1 Carer scored 3/6                                 |

Fig. 4

Carers questionnaire responses.

The anaesthetic was consultant-led and the same method was employed for all patients. Each patient underwent a general anaesthetic with a caudal epidural. The use of clonidine in the caudal helps reduce the use of morphine postoperatively and therefore facilitate the day case procedure.<sup>17,18</sup> Safety for same day discharge procedure was defined as: a patient who underwent an open reduction for DDH, reduction confirmed on postoperative imaging, minimal intraoperative blood loss, did not require fluid or blood resuscitation, and experienced no operation-related complications.

Feasibility for the day case surgery was defined as: a patient who underwent an open reduction for DDH, was deemed fit for same day discharge by the multi-disciplinary team, and expressed a positive subjective perspective in the feasibility questionnaire.

**Statistical analysis.** Data were extracted using a data collection table on Microsoft Excel (USA) and a descriptive data analysis was performed.

## Results

There were 168 consecutive surgical procedures for DDH during the study period. A total of 16 patients fitted the inclusion criteria: 81.3% female ( $n = 13$ ), 69% left hip ( $n = 11$ ), mean age 15.8 months (10 to 26). All patients followed the same selection criteria, treatment pathway, surgical technique, and discharge criteria. The demographics (age, laterality, sex), safety (short-term outcome, blood loss, complications, and readmissions), and feasibility data are presented in Table I.

The short-term outcomes for all cases based on post-operative imaging were adequate showing a concentric hip reduction. All cases were deemed safe for same day discharge based on the perioperative assessment described. Overall, 15 cases were deemed feasible according to the definition. The intraoperative blood loss for the patients ranged between minimal to 120 ml and no patient had immediate postoperative complications. Prior to discharge the patients were assessed with the FLACC score; all patients scored 0 and were therefore deemed feasible for discharge.

Two patients had complications: one experienced transient fever and vomiting which was self-limiting and was diagnosed as a viral infection, and the second developed chest blisters that evolved into a generalized rash, diagnosed as chickenpox. These two patients' overnight stay was documented as a complication unrelated to the surgery with neither requiring any intervention.

The carers' responses to the questionnaire is presented in Figure 4. All participants reported receiving adequate information about analgesia and spica cast management prior to discharge and 94% reported having sufficient information regarding day-to-day management to allow same day discharge. The one family who reported not receiving sufficient information was of the patient later diagnosed with chickenpox. Additional subjective feedback from the questionnaire included several carers reporting that the social media-based support groups were a useful resource for information and reassurance.

**Table 1.** Patient demographics and safety data.

| Variable (total patients n = 16)      | n               |
|---------------------------------------|-----------------|
| <b>Demographic characteristic</b>     |                 |
| Female sex, n (%)                     | 13 (81)         |
| Mean age, mths (range)                | 15.8 (10 to 26) |
| Laterality, left, n (%)               | 11 (69)         |
| <b>Safety</b>                         |                 |
| Blood loss, ml                        | Minimal* to 120 |
| Complications, n (%)                  | 2 (13%)         |
| Operation-related complications       | None            |
| Readmissions                          | None            |
| Confirmed reduction on imaging, n (%) | 16 (100)        |

\*Blood loss was assessed using the suction fluid bucket and the surgical swabs. In the case of an empty suction bucket and no difference in the weight of the surgical swabs the blood loss was recorded as "minimal".

## Discussion

This study found open reduction for DDH as a day case to be safe and feasible. The short-term outcomes of a reduced hip on the postoperative radiographs were met in all cases. The intraoperative blood loss was minimal with no indication for blood transfusion. There were no operation-related complications that resulted in delay in discharge. There were no readmissions or any unplanned input following discharge.

Regarding the two reported complications; neither of these patients required intervention for their symptoms. We consider these complications unassociated with the procedure, that they would likely have occurred despite the procedure, and could have occurred in any patient going through any other day case procedure. Indeed, these illnesses may have occurred at home the following day and were therefore still considered safe for a day case according to our definition.

Traditionally, patients would be admitted in hospital overnight for observation, postoperative imaging, and analgesia. The requirement for this has been reduced by careful planning, minimal blood loss, and better postoperative pain management. The development of perioperative pathways with multidisciplinary stakeholders allow for a more informed and efficient patient journey through the healthcare system both pre- and postoperatively. Conducting closed reduction for DDH as a day case at our centre is likely to have aided the acceptance and successful adoption of day case open reduction of DDH within the culture of the paediatric surgical and anaesthetic departments. There has also been a shift within the healthcare service following the COVID-19 pandemic, which encourages conducting more procedures as day cases in order to avoid unnecessary admission. This in turn reduces exposure of the individual to a hospital environment, increases bed capacity, and allows theatre staff to continue working in a familiar environment.<sup>19</sup>

Our day case stringent selection criteria allow us to identify children who are suitable for same day discharge.

Children with comorbidities may require more extensive pre- and postoperative care and monitoring, meaning they would not be safe for discharge on the day of surgery. In our study we considered patients having a simultaneous osteotomy too high-risk for same day discharge. However, a recent study from Ireland suggested it is safe for patients to have same day discharge after pelvic osteotomies in DDH children.<sup>20</sup> In this study 35 patients were selected for day case procedures, but they had seven patients who either failed same day discharge or returned to the emergency department requiring an inpatient stay. Even though this study reported a 20% readmission rate, it paves the way to consider including osteotomies for day case procedures as well.

An essential element of this process is support from parents. The feasibility scores by the parents show excellent support for day case procedure. All but one carer gave a score of 6/6 on the questionnaire. The outlier result in the questionnaire was 3/6 and the negative response was due to a poor day one experience. This patient had contracted chickenpox and the first postoperative day's experience was likely influenced by the unexpected additional morbidity.

Day case procedures offer a mutually beneficial approach in paediatric orthopaedic surgery. They have been shown to increase overall satisfaction for patient and family,<sup>7,8</sup> potentially reducing parents' absence from work, and with an obvious benefit to the healthcare provider by increasing efficiency and reducing costs.<sup>5,6,20</sup> There are also qualitative benefits of reducing the time carers spend away from home where they may have other children and the disruption that this would cause, especially in single parent households. These benefits are even more important in the present day, as the COVID-19 pandemic will affect the way elective surgery is delivered and a reduced length of hospital stay is likely to be safer with increased satisfaction for patients and their parents.

The limitations of this study include a small sample size of patients. This study was not designed to produce generalizable findings, however the context is transferable as it may be applicable to similar paediatric departments to replicate. The surgical procedure, anaesthetic approach, and postoperative care are not necessarily unique to our unit. This study does not aim to present a novel approach, rather merely confirming that this approach is safe to allow same day discharge. However, the recent Getting It Right First Time (GIRFT) report commented on the uniqueness of this day surgery approach following their visit to our centre.<sup>21</sup> To our knowledge, this is the first paper concerning the safety and feasibility of open reduction of DDH as a day case and represents an important early stage in the development of a day case standard of care protocol.

In conclusion, this study found that open reduction for DDH, without osteotomy, is safe and feasible to be



performed as a day case procedure with high level of family satisfaction. It requires a clear treatment pathway, appropriate patient selection as well as thorough counselling and communication with carers.

## Twitter

Follow Y. Gelfer @yaelgelfer

## References

- Dorn U, Neumann D.** Ultrasound for screening developmental dysplasia of the hip: a European perspective. *Curr Opin Pediatr.* 2005;17(1):30–33.
- Paton RW.** Screening in developmental dysplasia of the hip (DDH). *Surgeon.* 2017;15(5):290–296.
- No authors listed.** Newborn and infant physical examination (NIPE) screening programme handbook. Public Health England. 2020. <https://www.gov.uk/government/publications/newborn-and-infant-physical-examination-programme-handbook/newborn-and-infant-physical-examination-screening-programme-handbook> (date last accessed 9 June 2020).
- Wright J, Tudor F, Luff T, Hashemi-Nejad A.** Surveillance after treatment of children with developmental dysplasia of the hip: current UK practice and the proposed Stanmore protocol. *J Pediatr Orthop B.* 2013;22(6):509–515.
- Huang A, Ryu J-J, Dervin G.** Cost savings of outpatient versus standard inpatient total knee arthroplasty. *Can J Surg.* 2017;60(1):57–62.
- Aynardi M, Post Z, Ong A, Orozco F, Sukin DC.** Outpatient surgery as a means of cost reduction in total hip arthroplasty: a case-control study. *HSS J.* 2014;10(3):252–255.
- Elsobky S, Ahmad N, Qureshi M, Izzath W, Sadiq H.** Paediatric day case tonsillectomy: a safe, feasible and an economical way to treat patients—Yorkhill experience. *Scott Med J.* 2014;59(1):5–8.
- Kelly MP, Calkins TE, Culvern C, Kogan M, Della Valle CJ.** Inpatient versus outpatient hip and knee arthroplasty: which has higher patient satisfaction? *J Arthroplasty.* 2018;33(11):3402–3406.
- Lazic S, Boughton O, Kellet C, Kader D, Villet L, Rivière C.** Day-Case surgery for total hip and knee replacement: how safe and effective is it? *EFORT Open Rev.* 2018;3(4):130–135.
- Husted H, Lunn TH, Troelsen A, Gaarn-Larsen L, Kristensen BB, Kehlet H.** Why still in hospital after fast-track hip and knee arthroplasty? *Acta Orthop.* 2011;82(6):679–684.
- Rabbits JA, Groenewald CB, Moriarty JP, Flick R.** Epidemiology of ambulatory anesthesia for children in the United States: 2006 and 1996. *Anesthesia & Analgesia.* 2010;111(4):1–5.
- Barbier D, N'Dele D, Bennis M, Thevenin-Lemoine C, De Gauzy JS, Accadbled F.** Day surgery for anterior cruciate ligament reconstruction in children: a prospective study on feasibility and satisfaction. *J Child Orthop.* 2019;13(1):100–106.
- Zadeh HG, Catterall A, Hashemi-Nejad A, Perry RE.** Test of stability as an aid to decide the need for osteotomy in association with open reduction in developmental dysplasia of the hip. *J Bone Joint Surg Br.* 2000;82(1):17–27.
- No authors listed.** Steps later treatment of DDH and spica cast care. The Parents' Guide. 2016. <https://www.stepsworldwide.org/wp-content/uploads/2020/02/Hip-Surgery-and-Spica-Cast-Care-1.pdf> (date last accessed 9 June 2020).
- No authors listed.** Hip dysplasia (DDH). Steps. 2020. <https://www.steps-charity.org.uk/conditions/hip-dysplasia-ddh/> (date last accessed 9)AD
- Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S.** The FLACC: a behavioral scale for scoring postoperative pain in young children. *Pediatr Nurs.* 1997;23(3):293–297.
- de Beer DAH, Thomas ML.** Caudal additives in children—solutions or problems? *Br J Anaesth.* 2003;90(4):487–498.
- Lee JJ, Rubin AP.** Comparison of a bupivacaine-clonidine mixture with plain bupivacaine for caudal analgesia in children. *Br J Anaesth.* 1994;72(3):258–262.
- No authors listed.** Specialty guides for patient management during the coronavirus pandemic, clinical guide for the management of trauma and orthopaedic patients during the coronavirus pandemic. NHS England and NHS Improvement. <https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/C0274-Specialty-guide-Orthopaedic-trauma-v2-14-April.pdf> (date last accessed June 2020).
- Moore DM, Sheridan GA, Kelly PM, Moore DP.** Day-Case pelvic osteotomy for developmental dysplasia of the hip. *J Child Orthop.* 2020;14(6):508–512.
- No authors listed.** GIRFT appoints clinicians to lead new paediatric and neonatal workstreams. GIRFT. 2020. <https://www.gettingitrightfirsttime.co.uk/new-paediatric-and-neonatal-workstreams/> (date last accessed 22 April 2020).

### Author information:

- M. Flatman, BSc, MBBS, Core Surgical Trainee, Stepping Hill Hospital, Stockport, UK.
- B. H. Barkham, BMBS, bmedsci, MRCS, Specialist Registrar
- E. Ben David, MBBS, Foundation Doctor
- A. Yeo, FRCS (Tr & Orth), MBBS, BSc(Hons), Consultant Paediatric Orthopaedic Surgeon
- J. Norman, BSc, MBBS, FRCA, Consultant Anaesthetist St. George's University Hospitals NHS Foundation Trust, London, UK.
- Y. Gelfer, MD, PhD, FRCS, Consultant Paediatric Orthopaedic Surgeon, St. George's University Hospitals NHS Foundation Trust, London, UK; St. George's University of London, London, UK.

### Author contributions:

- M. Flatman: Contributed to the data collection and analysis, Contributed to drafting the manuscript.
- B. H. Barkham: Contributed to the data analysis, Drafted and edited the manuscript.
- E. Ben David: Contributed to the data collection, Edited the manuscript.
- A. Yeo: Contributed to the recruitment and data collection, Edited the manuscript.
- J. Norman: Conceptualized the study, Contributed to the data collection and anaesthetic protocol, Edited the manuscript.
- Y. Gelfer: Conceptualized the study, Contributed to data collection and analysis, Wrote and edited the manuscript.

### Funding statement:

- No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

### ICMJE COI statement:

- We have no disclosures of funding received from the National Institute of Health (NIH), Wellcome trust, Howard Hughes Medical Institute (HHMI) and others.

© 2021 Author(s) et al. This is an open-access article distributed under the terms of the Creative Commons Attributions licence (CC-BY-NC-ND), which permits unrestricted use, distribution, and reproduction in any medium, but not for commercial gain, provided the original author and source are credited.