Surgical and anesthetic considerations in histrelin capsule implantation for the treatment of precocious puberty

James S. Davis a, Fuad Alkhoury b, Cathy Burnweit b,c,*

a Department of Surgery, University of Miami Miller School of Medicine, Miami, FL
b Department of Pediatric Surgery, Miami Children’s Hospital, Miami, FL
c Department of Surgery, Herbert Wertheim College of Medicine, Florida International University, Miami, FL

Abstract

Precocious puberty treatment traditionally meant anxiety-provoking monthly depot injections until the advent of the annually implanted histrelin capsule. This study is the first to evaluate the surgical and anesthetic aspects of histrelin implantation for precocious puberty.

Methods: All cases from one surgeon at a tertiary pediatric hospital were reviewed for patient age, anesthetic type, technical difficulties, and complications.

Results: From 12/2007 to 3/2013, 114 cases (49% implantations, 25% removals/re-implantations, 25% removals) were performed. Local anesthesia was employed in 100% of non-general anesthesia cases (n = 109, 96%), augmented by inhaled N2O in 49%. Five patients (4%) underwent general anesthesia: three neurologically-impaired and two coordinated with scheduled MRIs. Procedural difficulties (n = 18, 16%) included implant fracture during removal (n = 16/58 removals, 28%). Fracture never occurred during implantation. Three children (3%) suffered complications. One infection was treated with antibiotics, and two implants were removed for systemic allergic reaction. Six children (5%) had unscheduled post-operative checks for pain (n = 3, 3%), allergy to elastic dressing (n = 2, 2%), or rash (n = 1, 1%).

Mean charges for implantations were $10,188 ± 1292 versus $528 ± 147 for N2O or local alone (p < 0.0001). Implants were removed for systemic allergic reaction. Six children (5%) had unscheduled post-operative checks for pain (n = 3, 3%), allergy to elastic dressing (n = 2, 2%), or rash (n = 1, 1%).

Conclusion: While histrelin implantation is straightforward, removal presents technical challenges. Local anesthesia, with possible N2O supplementation, is well-tolerated and introduces substantial resource and cost savings.

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device implantation and removal in most patients, thereby introducing substantial cost savings to both patient and hospital while controlling risk.

1. Methods

This retrospective study was approved by the hospital’s Institutional Review Board (#306359). We collected data regarding all subcutaneous histrelin implant cases handled between December 2007 and March 2013 by one pediatric surgeon (CB) at a tertiary care pediatric hospital. At the initial clinic visit, the family was counseled regarding the procedure and the options of general anesthesia in the main operating room or local anesthesia, with or without nurse-practitioner–administered conscious sedation with nitrous oxide (N₂O), in the minor procedure room [7]. For this latter venue, all children had eutectic mixture of local anesthetics (EMLA) placed on the skin at the insertion site prior to the operation, and a parent was invited into the suite with the child whether or not N₂O was used.

The capsules were deployed in the cephalad direction through a 4 mm incision in the medial aspect of the non-dominant arm, approximately two thirds of the way down, in the subcutaneous tissue overlying the groove between the biceps and the triceps. For implantations, the kit furnished by the manufacturer alone was used. It included lidocaine 1%, to which we added bicarbonate, all skin prep and drape materials, a disposable scalpel and hemostat, a capsule insertion “gun”, suture, gauze, steri-strips and dressing supplies. The capsule came separately in a sterile medication vile. For removals (or replacements), an instrument tray compiled by the hospital for minor procedures was employed, as significant dissection could be anticipated. Patient documentation, including procedure and clinic visit notes, was reviewed in detail. Demographic data, procedure type (placement, replacement or removal), anesthetic type, implantation location, time between implantation and retrieval, technical difficulties, complications and patient charges were collected. Based on the information, descriptive statistics were calculated, using mean ± standard deviation (SD) or median and interquartile ranges (IQR) where appropriate. A student’s t-test was used for parametric data, whereas a Mann–Whitney U test was used for non-parametric data—both tests with significance set to p ≤ 0.05.

2. Results

A total of 114 cases were performed. The mean patient age was 8.9 ± 1.8 years, with females outnumbering males by a 3:1 ratio. Of the cases, 49% (n = 56) were implantations, 25% (n = 29) were replacements (removal with re-implantation) and 25% (n = 29) were removals only. The median time between implantation and implant removal was 399 (IQR 80) days. Twenty-seven of the patients remained with the device implanted at the time of submission to the publisher. Demographic, procedural and anesthetic information on the cohort are presented in Table 1.

All patients undergoing operation in the procedure suite had the pre-operative EMLA removed followed by injection of lidocaine 1% with epinephrine buffered with bicarbonate as the standard initial local anesthetic regimen. This regimen alone was sufficient in 58 of the cases (51%). Another 56 subjects (49%) received supplemental N₂O, as planned preoperatively at the family’s request. Only five cases (4%) involved general anesthesia: three in cases of neurologic/behavioral impairment and two electively coordinated with scheduled magnetic resonance imaging exam. All patients tolerated the procedures, whether with local anesthesia, conscious sedation, or general anesthesia, and no patient required conversion to a stronger level of anesthesia once a procedure started. One child with severe autism initially refused to recline on the operating table and, although we completed the implantation with local anesthesia and conscious sedation, the family reluctantly acquiesced to general anesthetic for his two subsequent procedures.

Operative challenges were encountered in 18 patients (16%). Of the 58 implant removals – which included patients in both the replacement and removal groups – sixteen (28%) resulted in implant fracture (Fig. 1). A 4 mm counter-incision proximal to the original incision was used to remove parts of the implant in 9 of these cases. In the remaining 7 cases, no counter-incision was necessary. All broken implants were completely retrievable in the original surgical venue, using the same anesthetic technique already initiated, and without supplementary imaging. One obese patient’s implant, while intact and seemingly palpable pre-operatively, could not be located through the initial incision at the implantation scar, and a counter-incision was made 2 cm proximal to the original incision for removal. Lastly, one patient’s implant insertion was rendered more difficult due to his unruly behavior, as described above.

The incidence of fracture was further examined with respect to surgeon procedural experience and duration of subcutaneous

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic, procedural, and anesthetic information for 114 patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>8.9 ± 1.8 years</td>
</tr>
<tr>
<td>Gender (n, %)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31 (27.2%)</td>
</tr>
<tr>
<td>Female</td>
<td>83 (72.8%)</td>
</tr>
<tr>
<td>Procedure Type (n, %)</td>
<td></td>
</tr>
<tr>
<td>Implantation</td>
<td>56 (49.1%)</td>
</tr>
<tr>
<td>Removal and re-implantation</td>
<td>29 (25.4%)</td>
</tr>
<tr>
<td>Removal only</td>
<td>29 (25.4%)</td>
</tr>
<tr>
<td>Local Anesthesia (n, %)</td>
<td></td>
</tr>
<tr>
<td>EMLAa</td>
<td>109 (95.6%)</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>109 (100%)</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>56 (49.1%)</td>
</tr>
<tr>
<td>General Anesthesia</td>
<td>5 (4.4%)</td>
</tr>
</tbody>
</table>

* EMLA, Eutectic Mixture of Local Anesthetics.
implantation. There was no statistical difference in fracture rate between the first 50% of removals and the second 50% of removals (8.8% vs 18%, p = NS). Broken capsules were not implanted for statistically longer periods than unbroken capsules (median 408 days, IQR 73 vs 397, 78, p = NS).

Three patients (3%) suffered complications; one infection was effectively treated with antibiotics, and two implants were removed for significant systemic allergic reaction characterized by generalized rash and severe pruritus refractory to medical therapy. Interestingly, the two children had implantations within days of each other with both devices coming from the same manufacturer’s lot. Two months after reporting the adverse effects, we received a letter from the manufacturer that its investigation had turned up no further related cases [8]. Six additional children (5%) required unscheduled post-operative checks: three for pain (3%), two for allergy to the elastic procedures provided in the kit (2%), and one for rash that spontaneously resolved (1%). The post-operative pain complaints originated with a telephone call, and the children were seen the same day in follow-up. Infections were ruled out, and symptoms resolved without untoward sequelae. No implant migrations were noted nor were any extrusions through the skin or incision sites. No imaging studies were used to locate the device preoperatively.

The hospital charges for the single patient undergoing general anesthesia for histrelin capsule implantation alone (surgeon’s procedure time 9 min) were $10,551 versus $528 ± 147 for implant procedures conducted under local or local in combination with conscious sedation (p < 0.001).

3. Discussion

The histrelin capsule has demonstrated efficacy as a safe and effective treatment for precocious puberty [3,5]. The implant most closely resembles the Implanon device (Merck, New Jersey; NV Organon, Oss, The Netherlands), a contraceptive containing progestin etonogestrel also implanted subcutaneously via injection gun near the distal humerus. The largest studies on Implanon revealed 1%–2% complication rates with insertion, 3% with post-insertion bruising or pain, and 1.7% with removal [9,10]. The Implanon is virtually unbreakable with routine handling, however, unlike the histrelin capsule which is quite fragile at removal.

In this study and in the initial experience with the histrelin implant, serious complications were uncommon, and none was a threat to life or function. As noted, device fracture is an ongoing issue. Impalpability, another potential problem, was encountered in one of our patients. Migration, while not noted in our reported cohort, is another anticipated complication. During the study period, we did see a girl, operated elsewhere two years before, whose implant was placed high on the medial arm and ended up in an impalpable position in the axilla. While the device unfortunately has no radio-opaque markings, it was identifiable by ultrasound, and the family has elected to wait for an upcoming otorhinolaryngological procedure for us to retrieve the capsule at the same general anesthetic. As she has not undergone a procedure, she is not included in our data.

Our experience has borne out several technical tips. The implants should be placed superficially—ideally, just under the skin. This will not only avoid potentially devastating neurovascular injuries, but it is also particularly important as significant weight gain is a frequent consequence of the treatment, which makes a deep implant harder to palpate. In addition, the insertion gun, used as directed, places the implant almost a centimeter away from the skin incision. Because the device becomes soft and easily damaged even with gentle handling and is frequently encased in a dense capsule over time, we prefer to leave the end of the implant nearer to the incision to make extraction easier. This modification might theoretically increase the risk of extrusion, and we therefore close the incision in layered fashion, using first a subcutaneous and then a subcuticular stitch with the suture included in the kit. Finally, we place the incision two-thirds of the way down the medial arm where the subcutaneous layer tends to be thinner, deploying the initial implant in a cephalad direction. This position allows us, if extensive dissection must be used to retrieve an implant during a replacement procedure, to have room above the elbow to place the subsequent implant distally through undisturbed tissue using the same wound.

Our operative experience with the histrelin implant compares favorably with previously published reports. In the two most recent papers, implant site reactions were common, occurring in 55% of implantations. Rates of ultrasound localization (6%) and scar formation (3%) exceeded our totals [3,4]. In one case, a suture was inserted directly into the implant, and one implant extruded during the pilot study [6]. Breakage during removal occurred only 18% of the time, a lower percentage than in our series, although existing reports provide no technical information regarding removals, and the number of cases is small. This major technical challenge, device fracture with handling, might be expected to relate to the implant’s subcutaneous duration, with increasing brittleness noted as the duration of implantation lengthens. Our results, however, do not demonstrate any statistically significant association.

For nearly 30 years, conscious sedation using N2O has been advocated for minor pediatric procedures. Initially described in 1981 [11], the technique has become widely used alone and in combination with other agents [12]. The multifaceted rationale for using conscious sedation, where appropriate, has been addressed elsewhere, but includes a lower risk profile, painless patient experience, no need for an empty stomach, and greater time and resource efficiency [7,13]. We suggest similar applicability for histrelin implant placement and removal. Lewis et al. also describe using local anesthesia and distraction techniques in an outpatient setting for histrelin procedures, while other studies report anesthetic approaches which vary by institution [3,14]. None of the previous studies, however, provided specifics regarding the ratio of local to general anesthesia, outpatient center to operating room usage or cost data. Generally, we recommend the initial placement under local anesthesia alone while advising conscious sedation for the removals or replacement in anticipation of the degree of dissection often required. The parents and children themselves, where mature enough, are involved in these decisions.

Our study is currently the largest series of histrelin capsule procedures reported to date, representing a single surgeon, single institution experience. Its retrospective design, however, has limitations with both recall and misclassification biases. Prospective studies would better establish acceptable complication rates. Whether placement by non-pediatric surgeons is a viable option also remains to be studied. A number of pediatric endocrinologists who began doing their own patients’ implantations immediately following FDA approval have since stopped because of the technical difficulties involved, particularly with removal [15].

Our report demonstrates that while implantation of the histrelin capsule is straightforward, retrieval presents challenges. Nevertheless, general anesthesia is not routinely necessary. Local injection, with or without conscious sedation, is sufficient for most patients, preserving general anesthesia for special circumstances. The avoidance of general anesthesia in the operating room setting reduces risk and introduces substantial resource and cost savings to both patient and hospital.

References


