The pharmacokinetics and safety of an intraoperative bupivacaine-collagen implant (XaraColl®) for postoperative analgesia in women following total abdominal hysterectomy

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Background: XaraColl®, a collagen-based intraoperative implant that delivers bupivacaine to the site of surgical trauma, is under development for postoperative analgesia. We examined the pharmacokinetics, safety and efficacy of XaraColl following implantation in women undergoing total abdominal hysterectomy.

Methods: Three XaraColl implants, each containing 50 mg bupivacaine hydrochloride, were implanted in 12 women undergoing total abdominal hysterectomy for a benign condition. Serum samples were obtained through 96 hours for pharmacokinetic analysis. Patients received acetaminophen 1000 mg every 6 hours, diclofenac 50 mg every 8 hours, and were given access to intravenous morphine for breakthrough pain via patient-controlled analgesia during the first 24 hours. Pain intensity was assessed at regular intervals using a 100 mm visual analog scale. Safety was assessed through 30 days.

Results: The pharmacokinetic profile displayed a double peak in bupivacaine concentration with the second peak occurring up to 24 hours after the first and at a generally higher concentration. The time to maximum concentration (tₘₐₓ) varied from 0.5 to 24 hours (median 12 hours) according to which peak predominated. The mean maximum concentration (Cₘₐₓ) was 0.22 µg/mL and the maximum individual Cₘₐₓ was 0.44 µg/mL, which are well below the established systemic toxicity threshold. Morphine use was generally low (mean 16.8 mg; median 6.5 mg) and compared favorably with institutional experience. At 6 hours post-surgery, 11 patients recorded pain scores ≤20 mm, 6 recorded ≤10 mm, and 2 reported no pain. Scores continued to decline throughout the study. The product was considered safe and well tolerated.

Conclusion: XaraColl exhibits a biphasic and sustained release profile that may provide a significant advance over standard wound infiltration. Considering the encouraging results from this study alongside those from other randomized controlled efficacy trials, XaraColl should be further evaluated as a postoperative analgesic in large, double-blind efficacy trials.

Keywords: pain, opioid use, analgesia, anesthetic

Introduction

Intraoperative wound infiltration with local anesthetics has been recommended as part of multimodal analgesia regimens for the management of postoperative pain following a variety of surgical procedures, including laparoscopic cholecystectomy, open hernia repair, abdominal hysterectomy, and knee replacement. However, other authors acknowledge that studies investigating the benefits of the technique have given mixed results and the literature is confusing. Locally acting drug delivery systems that can be administered intraoperatively and further sustain the period of postoperative...
analgesia could potentially offer significant advantages over bolus infiltration and be effective over a much wider range of surgical procedures.

One such product is Exparel® (Pacira Pharmaceuticals, Parsippany, NJ), a liposome injection of bupivacaine for single-dose infiltration into the surgical site that was recently approved for sale in the United States. Other products currently in development include Posidur® (Durect Corporation, Cupertino, CA), an injectable viscous depot of bupivacaine based on sucrose acetate isobutyrate, and XaraColl® (Innocoll Technologies, Athlone, Ireland) (Figure 1), a biodegradable and fully resorbable collagen-based matrix that is designed to release and deliver bupivacaine for local, sustained action at the site(s) of surgical trauma. Randomized controlled trials performed in women undergoing open gynecological surgery and in men undergoing hernioplasty have concluded that XaraColl is effective in reducing patient use of opioid analgesia and/or their pain intensity for up to 3 or 4 days postoperatively. The product also offers great versatility and is already proven suitable for use in laparoscopic surgery. The primary objective of this study was to characterize XaraColl’s pharmacokinetic profile and elucidate its mechanism of drug release in vivo.

**Research design and methods**

We performed a prospective study in women undergoing total abdominal hysterectomy to assess the pharmacokinetics, safety and tolerability of XaraColl (EudraCT No: 2005-003748-73). The study was performed at Wexham Park Hospital, Slough, United Kingdom (UK), in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines following United Kingdom (UK), in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines following UK Medicines and Healthcare products Regulatory Agency (MHRA).

Eligible patients included women aged 18 to 60 years and weighing 60 to 95 kg who were scheduled for total abdominal hysterectomy with or without bilateral salpingo-oophorectomy, for a benign condition. Patients with uterine adenocarcinoma, cervical cancer, leiomyosarcoma or a suspicion of these cancers were excluded. We also excluded patients with hypersensitivity to amide anesthetics, those taking drugs which might affect the efficacy of the anesthetic, those having any clinically significant, unstable cardiac, neurological, immunological, renal or hematological disease, as well as anyone who had been hemodynamically unstable within the previous 4 weeks, had hepatic impairment, or had any other condition that in the opinion of the investigator would interfere with the course of the study.

Patients were screened within 14 days of enrolment, which included a full medical history and physical examination, baseline observations, an electrocardiogram and baseline blood tests. Those who met eligibility requirements reviewed and signed the informed consent form.

Surgery was conducted under general anesthesia. The use of epidural anesthesia or local anesthetic infiltrations was prohibited. Three XaraColl implants, each containing 50 mg bupivacaine hydrochloride, were implanted at different levels in the surgical wound. The implants were first divided into 3 strips before being placed over the vaginal vault (Figure 2A), along the line of peritoneal closure (Figure 2B) and along the rectus sheath incision (Figure 2C). The thickness of the collagen matrix shrinks on absorption of fluid, which ensures that there is no compression of adjacent structures. Time 0 was defined as the time of implantation of the first XaraColl implant.

The postoperative analgesic regimen was multimodal. Patients received oral acetaminophen 1000 mg every 6 hours, oral diclofenac 50 mg every 8 hours, and had access to intravenous morphine via patient-controlled analgesia for the first 24 hours post-surgery as needed to control breakthrough pain. All strong or moderate CYP3A4 pathway inhibitors (including grapefruit juice) or inducers were prohibited and no analgesics were permitted in the 24 hours prior to the study commencing.

**Pharmacokinetic assessments**

Serum samples for pharmacokinetic analysis were obtained at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 18, 24, 36, 48, and 72 hours after Time 0. The bupivacaine hydrochloride was extracted from the plasma with diethyl ether and assayed using a HPLC method with a validated quantification range from 0.001 µg/mL to 0.500 µg/mL. The individual plasma concentrations of bupivacaine were tabulated for each
sampling time and summarized descriptively. Bupivacine plasma-concentration time profiles were analyzed using model-independent methods in WinNonlin™ (version 5.2; Pharsight, Sunnyvale, CA, USA).

Efficacy assessments
We recorded the amount of intravenous morphine administered by patient-controlled analgesia during the first 24 hours as a measure of breakthrough pain. Patients also assessed their pain intensity at 1, 1.5, 2, 3, 6, 9, 12, 18 (if awake), 24, 36, 48, 72 and 96 hours after Time 0 using a horizontal visual analog scale with the left anchor (0 mm) labeled “no pain” and the right anchor (100 mm) labeled “as bad as it could be”. The data obtained were summarized descriptively.

Safety assessments
Vital sign assessments were performed at the same time as the pharmacokinetic sampling. Blood samples for safety analysis were obtained at 6, 24, 48, 72, and 96 hours, and a full physical examination was performed on day 3. All adverse events occurring within 30 days were recorded and classified by the investigator according to intensity and relationship to study drug. Patients were regularly evaluated for physical signs of bupivacaine toxicity such as oral tingling, tunnel vision and breathing difficulties. Safety data was summarized descriptively and no formal statistical analysis was performed.

Results
We enrolled 13 women between January 19, 2007 and July 20, 2007. Twelve patients completed the study and one (patient no 8) was withdrawn by the investigator after screening, but before surgery and XaraColl implantation, for failing to comply with the inclusion/exclusion criteria. The disposition of all enrolled patients is summarized in Figure 3 and patient demographics are presented in Table 1.

Pharmacokinetics
The mean and individual pharmacokinetic profiles are presented graphically in Figures 4 and 5, respectively, and the corresponding pharmacokinetic parameters are summarized in Table 2. The mean maximum concentration ($C_{\text{max}}$) of bupivacaine hydrochloride was 0.22 µg/mL (range 0.14 µg/mL to 0.44 µg/mL). A particularly distinctive feature
was an apparent double peak in the bupivacaine concentration-time profiles of the individual patients. Consequently, the time to maximum concentration ($t_{\text{max}}$) ranged from 0.5 hours to 24 hours (median 12.0 hours; mean 12.5 hours) according to whether the early or late peak predominated. For most patients, this was the late peak. However, in the case of Patient 12, the late peak (0.19 µg/mL at 24 hours) was marginally lower than the early peak (0.20 µg/mL) recorded at 0.5 hours.

**Efficacy**

The total amount of intravenous morphine administered by each patient via patient-controlled analgesia is presented in Figure 6 (range 0 to 74 mg). The mean usage was 16.8 mg (median 6.5 mg; standard deviation 24.4 mg). We noted two outliers within these 12 patients. One who had a history of chronic pelvic pain administered 74 mg and another, who reported using the morphine to control a pre-existing back pain condition, administered 57 mg. If both these outliers are excluded, the mean usage was 7.1 mg (median 4.0 mg; standard deviation 8.8 mg; range 0 to 28 mg). No patient took opioid analgesics after the first 24 hours once the patient-controlled analgesia had been discontinued.

Because opioid consumption is a cofounding factor in the measurement of pain scores, we have also included patients’ self-assessments of their pain intensity at 6, 24, 48 and 72 hours in the same figure. For example, it is possible for patients to report low pain scores as a consequence of self-administering high amounts of opioid analgesics. However, Figure 6 confirms that low pain scores were reported by even those patients who used very low amounts of morphine. After only 6 hours, 11 patients (92%) recorded visual analog scores ≤ 20 mm on a scale from 0 to 100 mm, of which 6 patients (50%) recorded ≤ 10 mm and 2 patients (17%) reported no pain. By 24 hours, 9 patients (75%) recorded ≤ 10 mm with 3 patients (25%) reporting no pain. Pain intensity continued to decrease beyond 24 hours after discontinuation of all opioid rescue medication and by 48 hours, 11 patients (92%) recorded ≤ 10 mm with 7 patients (58%) reporting no pain. The mean pain score over time is profiled in Figure 7.

**Safety**

There were a total of 42 adverse events with each patient recording at least one. All adverse events reported as

![Figure 4](https://www.dovepress.com/submit-your-manuscript)
mild or moderate in intensity and all resolved. Twenty-three of the events were as a result of abnormal clinical laboratory investigations, of which the overwhelming majority were considered to be a consequence of undergoing the hysterectomy procedure itself and therefore unrelated to XaraColl. These included abnormal laboratory values for the following parameters: hemoglobin, white blood cells, neutrophils, platelets, prothrombin time (PT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein, phosphate measurements, and also blood found in the urine. Generally, blood chemistry parameters showed no obvious change during the study. The exception was C-reactive protein, an indicator of inflammation, which showed progressively increasing concentrations as expected after major surgery. Unrelated adverse events that were reported by more than one patient are summarized in Table 3.

Four patients had abnormal laboratory results that the investigator considered possibly related to XaraColl. One patient had slightly elevated ALT and AST levels, one patient had slightly elevated AST levels, and one patient had slightly decreased phosphorus levels; none of which were considered clinically significant and resolved without treatment. The other patient had two slightly elevated phosphorus levels during the study that the investigator felt were possibly related to XaraColl, however, this patient also showed a similarly elevated phosphorus level at screening.

Two other adverse events were also considered possibly related to XaraColl. One patient had moderate bruising on her abdomen that was coded as “contusion” and resolved without intervention. The other patient reported “visual disturbance” that was considered moderate in intensity. This was the only adverse event that could possibly be an indicator of bupivacaine toxicity. The event lasted for approximately one hour before resolving fully without intervention and this patient had very low systemic exposure to bupivacaine; her $C_{\text{max}}$ was 0.15 $\mu$g/mL.

One serious adverse event was reported during the study. A 45 year old obese patient was readmitted to the hospital with moderate wound dehiscence and moderate infection.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
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<tbody>
<tr>
<td>$C_{\text{max}}$ ($\mu$g/mL)</td>
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<td>0.22</td>
<td>0.08</td>
<td>0.14</td>
<td>0.44</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (hours)</td>
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<td>12.5</td>
<td>5.7</td>
<td>0.5</td>
<td>24.0</td>
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<tr>
<td>$t_{1/2}$ (hours)</td>
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<td>7.9</td>
<td>12.6</td>
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<tr>
<td>$\text{AUC}_{\text{last}}$ (µg h/mL)</td>
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<td>6.53</td>
<td>2.25</td>
<td>4.06</td>
<td>10.69</td>
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<tr>
<td>$\text{AUC}_{\text{inf}}$ (µg h/mL)</td>
<td>5.62</td>
<td>6.36</td>
<td>2.23</td>
<td>4.07</td>
<td>10.71</td>
</tr>
</tbody>
</table>

Abbreviations: $C_{\text{max}}$, maximum concentration; $t_{\text{max}}$, time to maximum concentration; $t_{1/2}$, terminal half-life; $\text{AUC}_{\text{last}}$, area under the plasma concentration–time curve from time zero to time of last measurable concentration; $\text{AUC}_{\text{inf}}$, area under the plasma concentration–time curve from time zero to infinity.

Figure 5 Individual plasma bupivacaine hydrochloride levels over time (reported in ng/mL).
The patient was treated with intravenous antibiotics and the wound was not re-sutured. The event resolved without sequelae and was considered unrelated to the study drug.

**Discussion**

Postoperative pain has been identified as the most common concern of surgical patients, yet despite widely accepted treatment standards and guidelines, is often undermanaged. Multimodal approaches to postoperative pain management have become the standard of care, although opioid analgesia continues to dominate most regimens.

Acute postoperative pain following abdominal hysterectomy can be quite severe and is generally considered multifactorial involving incisional pain, visceral pain from deeper structures, and dynamic pain such as that associated with straining, coughing or mobilizing. However, visceral pain has been reported to dominate during the first 48 hours after hysterectomy.

The use of intraoperative bupivacaine administered in bolus fashion to infiltrate the tissue around the surgical incision and/or for intraperitoneal administration has been widely investigated in patients undergoing hysterectomy. The results of these trials have been mixed, with some researchers reporting a clinical benefit, but most concluding otherwise. However, other studies have demonstrated postoperative analgesia when the hysterectomy wound is infiltrated with bupivacaine via a catheter postoperatively; either continuously or by patient control. We therefore hypothesized that by implanting XaraColl at different depths within the surgical cavity, we could beneficially achieve sustained analgesia for both the visceral and incisional pain components.

The prescribing information for bupivacaine hydrochloride injection recommends a bolus dose of up to 150 mg for wound infiltration, with no more than 400 mg in 24 hours. Bupivacaine overdose is associated with central nervous system and cardiovascular system toxicities. In pharmacotoxicity studies, the seizure threshold in Rhesus monkeys occurred at a mean plasma concentration of 4.5 µg/mL and convulsive plasma concentrations in sheep were observed at 10 µg/mL and 2.5 µg/mL by intravenous bolus and slow infusion, respectively. An intravenous infusion study in healthy volunteers and dogs indicated that the convulsive dose in dog corresponded to a mean plasma concentration of at least 4.0 µg/mL, and that 2.1 µg/mL was subconvulsive in humans. In another intravenous infusion study, 14 healthy volunteers were administered bupivacaine at 10 mg/min until the first signs of central nervous system toxicity. The mean C\text{max} recorded when infusion was stopped, or shortly thereafter, was 2.25 µg/mL. According to the

![Figure 6](https://www.dovepress.com/)
**Figure 6** Total morphine administered by patient-controlled analgesia (PCA) and visual analog scale (VAS) scores at 6, 24, 48 and 72 hours for individual patients. **Note:** Patient 8 was withdrawn by the investigator before surgery.

![Figure 7](https://www.dovepress.com/)
**Figure 7** Mean visual analog scale (VAS) score with standard deviation over time.
Unrelated adverse events reported by more than 1 patient

<table>
<thead>
<tr>
<th>Adverse event preferred term (MedDRA coded)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>C-reactive protein increased</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>White blood cell count increased</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Back pain</td>
<td>2 (16.7)</td>
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</table>

Abbreviation: MedDRA, Medical Dictionary for Regulatory Activities.

literature, central nervous system toxicity is usually evident before the appearance of cardiovascular toxicity, but with these events rarely seen in humans at plasma levels below 2.0 µg/mL and 4.0 µg/mL, respectively.

In pharmacokinetic studies involving bolus wound infiltration, the t_{max} for bupivacaine is rapid. For example, in a pharmacokinetic study at a 100 mg dose, the t_{max} in 12 men undergoing inguinal herniorrhaphy ranged from only 0.25 to 2 hours. In a similar herniotomy study in 12 children at a dose of 1.25 mg/kg, the mean (standard deviation) t_{max} was only 14.6 (7.2) minutes and in another study in 11 patients undergoing knee arthroscopy, the mean (standard deviation) t_{max} was 43.4 (23.1) minutes following 100 mg administered intra-articularly. However, despite the rapid systemic uptake, the mean C_{max} remained well below the toxicity threshold at these relatively low bolus doses. For example, in the aforementioned pharmacokinetic studies, the mean (standard deviation) C_{max} was relatively constant for these equivalent doses at 0.47 (0.33) µg/mL, 0.36 (0.14) µg/mL, and 0.48 (0.20) µg/mL, respectively. From a safety perspective, however, it is important to also consider the maximum individual C_{max}, which was 1.14 µg/mL in the herniotomy patients, i.e., 57% of the plasma concentration at which onset of toxicity may be expected in some patients.

Our pilot study was designed to evaluate the systemic pharmacokinetics of three XaraColl implants (each containing 50 mg bupivacaine hydrochloride; 150 mg total dose) inserted intraoperatively at different depths in the pelvic cavity. The primary aim was to characterize XaraColl’s pharmacokinetic profile, particularly in terms of C_{max} for estimating future dose limitations. We found a mean (standard deviation) C_{max} of 0.22 (0.08) µg/mL, with a maximum individual of 0.44 µg/mL (i.e., only 22% of the accepted lower toxicity threshold). Of note is that the mean C_{max} in this study compares favorably with the 0.14 µg/mL we observed in another study where two XaraColl implants (100 mg total dose) were inserted in men undergoing open inguinal herniotomy (Innocoll Technologies, data on file, 2009). This, along with the corresponding area under the curve (AUC) data, confirms that XaraColl exhibits proportional and predictable kinetics across these different doses, surgeries, and genders. Based on these pharmacokinetics, we conservatively estimate that XaraColl doses up to 450 mg could be administered in future studies without expecting plasma concentrations in excess of those resulting from a 150 mg bolus infiltration. Such a dose would also be reasonably in line with the maximum 400 mg (with epinephrine 1:200,000) dose recommended for wound infiltration in 24 hours.

Another salient feature of the pharmacokinetics was the apparent double peak in the bupivacaine concentration-time profile. This was observed in the majority of individual patients, with the first peak generally occurring within the first 2 hours and the second between 12 and 24 hours. One possibility is that the drug was being released and/or systemically absorbed at different rates according to the site/depth of implantation. However, this explanation is unlikely since the same double-peak phenomenon is subject to a patent application and was clearly evident in an earlier preclinical study where only one 50 mg XaraColl implant was used in beagle dogs. We also observed a similar double peak in patients undergoing open inguinal herniotomy who received two 50 mg XaraColl implants (Innocoll Technologies, data on file, 2009). Therefore, based on the body of evidence, XaraColl seems to exhibit a biphasic drug release profile in vivo; with an early, fast release phase followed by a subsequent, sustained release phase.

The mean (standard deviation) terminal half-life (t_{1/2}) we observed for bupivacaine in this study was 10.1 (1.8) hours. This compares with only 3.1 (1.4) hours reported for bolus intra-articular infiltration and 2.7 hours in adults following injection for nerve block. It is therefore reasonable to assume that some drug is still being slowly absorbed even as the plasma concentration decays following the second peak. This, in turn, suggests that the implant continues to release bupivacaine well after the first 24 hours, and so can sustain the local action.

We believe that the biphasic release profile we observed in this and other XaraColl studies is a highly desirable feature for this type of product. The early peak provides an initial burst of drug to target the immediate postoperative pain. Bupivacaine itself has a relatively long duration of action (approximately 200 minutes after bolus infiltration) to maintain this local analgesia through the first few hours when pain is normally at its worst. Thereafter, there is a slow release phase which can sustain the local concentrations and provide analgesia through at least 48 hours. Such a mechanism is consistent with results from our controlled efficacy trials that have demonstrated analgesia through...
72 hours postoperatively in patients undergoing open inguinal hernioplasty and gynecological surgeries.\textsuperscript{3,4}

Although it was not a randomized controlled trial, we believe that the women in this study benefited from the treatment and points to XaraColl’s probable efficacy in this indication. Notably, the patients generally reported low levels of pain intensity. For example, only 6 hours after their surgery, 92% recorded ≤ 20 mm on a visual analog scale from 0 to 100 mm, 50% recorded ≤ 10 mm, and 17% recorded no pain. These scores were achieved despite a median morphine dose of only 6.5 mg (range 0 to 74 mg) administered intravenously via patient-controlled analgesia in the first 24 hours. Indeed, the morphine used by our XaraColl-treated patients was considerably lower than comparative data (median 32 mg; range 22 to 90 mg) retrospectively obtained from another group of 12 patients who underwent surgery at the same hospital, but did not volunteer for the trial. Furthermore, once patient access to intravenous morphine was discontinued at 24 hours after surgery, pain scores recorded by the patients in our study continued to decline. By 48 hours after surgery, 92% recorded scores ≤ 10 mm with 58% reporting no pain. Consequently, patients were mobilized earlier than typically experienced at our institution following this type of major gynecological surgery.

There are several limitations of our study. Firstly, it was a pilot study in 12 subjects aimed primarily at obtaining safety and pharmacokinetic data; therefore a control group was not included. The efficacy assessments were only performed to provide some preliminary comparisons with patients undergoing similar surgeries at the same institution and to complement data from other companion randomized controlled trials. Secondly, while the results provide a preliminary pharmacokinetic profile, a definitive study that includes a range of doses and populations, such as elderly patients or those with hepatic impairment, is necessary to confirm XaraColl’s safety over a wide variety of patients.

**Conclusion**

The pharmacokinetic profile of XaraColl displays a distinctive double peak in bupivacaine plasma concentration, with the second peak occurring up to 24 hours after the first and generally at a higher concentration. This is indicative of a biphasic drug release profile and offers a unique mechanism for the provision of sustained postoperative analgesia. Compared to bolus methods of wound infiltration, the time to maximum concentration is considerably extended and the maximum concentration is significantly reduced. Consequently, much higher bupivacaine doses can be administered at the time of surgery without increasing the risk of neurotoxicity or cardiotoxicity.

Intuitively, by coupling the pharmacokinetic advantages with the ability to specifically target the surgically traumatized tissues that cause both visceral and incisional pain, XaraColl represents a significant advance over standard wound infiltrations that are sometimes used as part of multimodal regimens for postoperative analgesia. Encouraging results from randomized controlled trials have already demonstrated preliminary evidence of efficacy, which is further supported by patients’ exceptionally low pain scores and demand for opioid rescue medication observed in this study. Taking these trials together, XaraColl seems to offer great versatility and promise as a postoperative analgesic, which should be further evaluated in large, double-blind efficacy trials.

**Acknowledgments**

This study was fully funded by Innocoll Technologies Ltd (Athlone, Ireland), and coordinated by ICON Development Solutions Ltd (Manchester, UK) who monitored the site, managed the clinical database, determined the bupivacaine concentrations in the serum samples, analyzed the data, and wrote the study report.

**Disclosure**

Mr Philip Reginald was the principal investigator and received research funding from Innocoll Technologies Ltd (Athlone, Ireland). Mrs Cusack is a paid consultant to Innocoll Technologies. The authors report no other conflicts of interest in this work.

**References**