Published Evidence Demonstrating the Causation of Glenohumeral Chondrolysis by Postoperative Infusion of Local Anesthetic Via a Pain Pump

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Background: Glenohumeral chondrolysis is the irreversible destruction of previously normal articular cartilage, occurring most commonly after shoulder surgery in young individuals. The reported incidence of this complication has risen rapidly since the early 2000s. As chondrolysis cannot be reversed, its occurrence can only be prevented by establishing and avoiding its causes.

Methods: We analyzed all published cases of glenohumeral chondrolysis, including the relevant published laboratory data, to consolidate the available evidence on the causation of this complication by the postoperative intra-articular infusion of local anesthetic via a pain pump.

Results: Analysis of the published evidence demonstrated a causal relationship between the infusion of local anesthetic and the development of glenohumeral chondrolysis. The risk of this complication in shoulders receiving intra-articular infusions via a pain pump was significantly greater with higher doses of local anesthetic: twenty of forty-eight shoulders receiving high-flow infusions developed chondrolysis, whereas only two of twenty-five shoulders receiving low-flow infusions developed this complication (p = 0.0029). Eleven of twenty-two shoulders receiving 0.5% bupivacaine developed chondrolysis, whereas none of six shoulders receiving 0.25% bupivacaine developed this complication (p = 0.05). Of twenty-two shoulders infused with 0.5% bupivacaine, the eleven that developed chondrolysis had a mean pain pump delivery volume of 377 mL, whereas the eleven that did not develop chondrolysis had a mean volume of 187 mL (p = 0.003). Among shoulders in which an intra-articular pain pump was used, the risk of chondrolysis was significantly greater when suture anchors were placed in the glenoid for labral repair (p < 0.001).

Conclusions: The published evidence indicates that the preponderance of cases of glenohumeral chondrolysis can be prevented by the avoidance of the intra-articular infusion of local anesthetic via a pain pump.
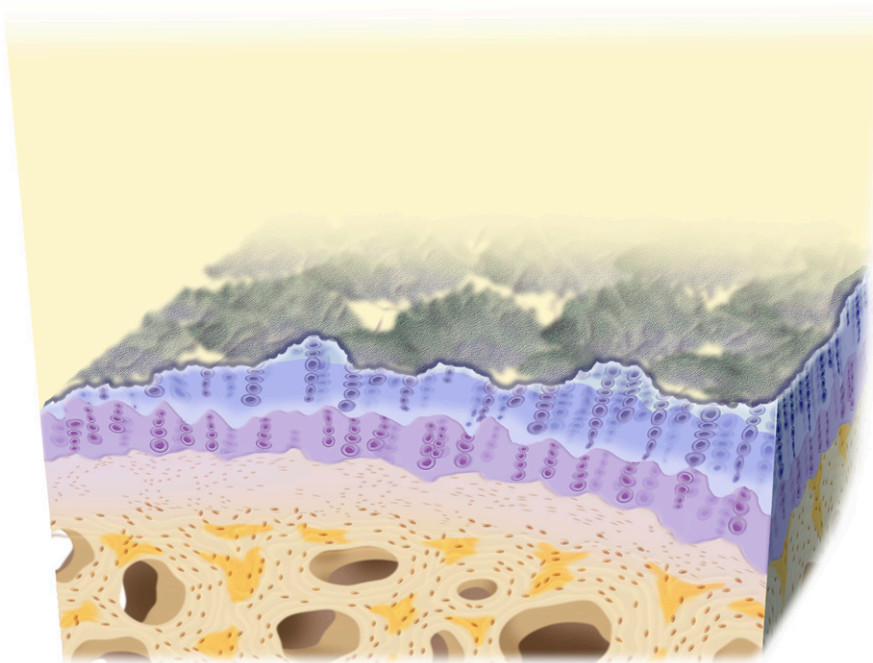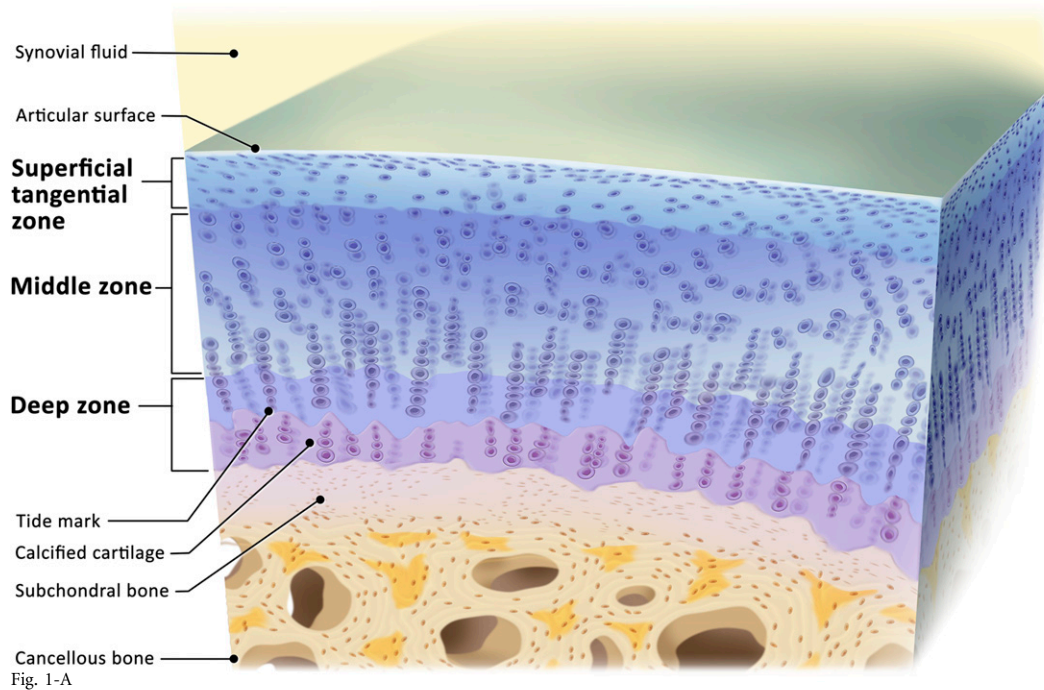
Level of Evidence: Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Glenohumeral articular cartilage consists of a collagen and proteoglycan matrix maintained by chondrocytes, which comprise only 1% of the total tissue (Fig. 1-A)[1-3]. Glenohumeral chondrolysis is the irreversible destruction of previously healthy articular cartilage resulting from the loss of the chondrocytes that maintain the intercellular matrix (Fig. 1-B)[1-13]. Glenohumeral chondrolysis cannot be reversed, and once initiated, it usually progresses to the complete loss of the articular cartilage.

There have been many published reports of shoulders that developed glenohumeral chondrolysis following the use of a pain pump for the intra-articular infusion of local anes-

thetic[14-28]. A 2010 systematic review of the 100 previously published cases of glenohumeral chondrolysis revealed that fifty-nine of these cases involved a combination of arthroscopic surgery and post-arthroscopic infusion of local anesthetic[26]. The number of cases reported is increasing rapidly; eighty-nine new cases were reported in 2011, with the majority of these being associated with the intra-articular infusion of local anesthetic[18,28]. There have also been many published laboratory studies demonstrating the toxic effects of local anesthetics on chondrocytes[4-8,11-13,29-44]. Against this background, it is surprising that two current concept reviews published in major

Fig. 1-A

Fig. 1-B

Figs. 1-A and 1-B Diagrammatic cross-sections of articular cartilage. **Fig. 1-A** Intact. **Fig. 1-B** Chondrolysis.

orthopaedic journals within the last two years concluded that the causes of this condition were only "speculative": "Despite considerable speculation among clinicians and researchers about the causal pathways and etiologic contributors associated with chondrolysis, definitive answers remain elusive,"[45] and "In the reported cases, no cause of PAGCL [postarthroscopic glenohumeral chondrolysis] has been confirmed, and the associations are mostly speculative."[46]

Because this stated uncertainty regarding the causation of glenohumeral chondrolysis by local anesthetic infused via a pain pump is reminiscent of the uncertainty regarding the causation of lung cancer by cigarette smoking over four decades ago, we used an approach similar to that proposed by Hill for rigorously establishing causal relationships in such contexts[47]. As we do today, Hill recognized the prohibitive ethical problems of performing prospective, randomized,

controlled clinical trials when causation appears likely. Therefore, he asked, "What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?" He listed nine: the strength of the observed association, the consistency of the association, the specificity of the association, the temporal relationship of the association, the existence of a biological gradient, biological plausibility, coherence of the evidence, experimental evidence, and analogy. Once the evidence in these nine dimensions was documented, Hill then asked, "is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?"

Our goal was to consolidate and present the considerable published evidence regarding the causation of glenohumeral chondrolysis by the intra-articular infusion of local anesthetic, in the hope that future cases of joint destruction from this etiology can be prevented without further speculation. We hypothesized that the published evidence relating chondrolysis to the use of intra-articular infusion of local anesthetic would meet the nine criteria for causation established by Hill.

Materials and Methods

In May 2012, we performed a literature search in PubMed, *The Journal of Bone and Joint Surgery* (American and British Volumes), *Arthroscopy: The Journal of Arthroscopy and Related Surgery*, *The American Journal of Sports Medicine*, *Clinical Orthopaedics and Related Research*, the *Journal of Orthopaedic Research*,
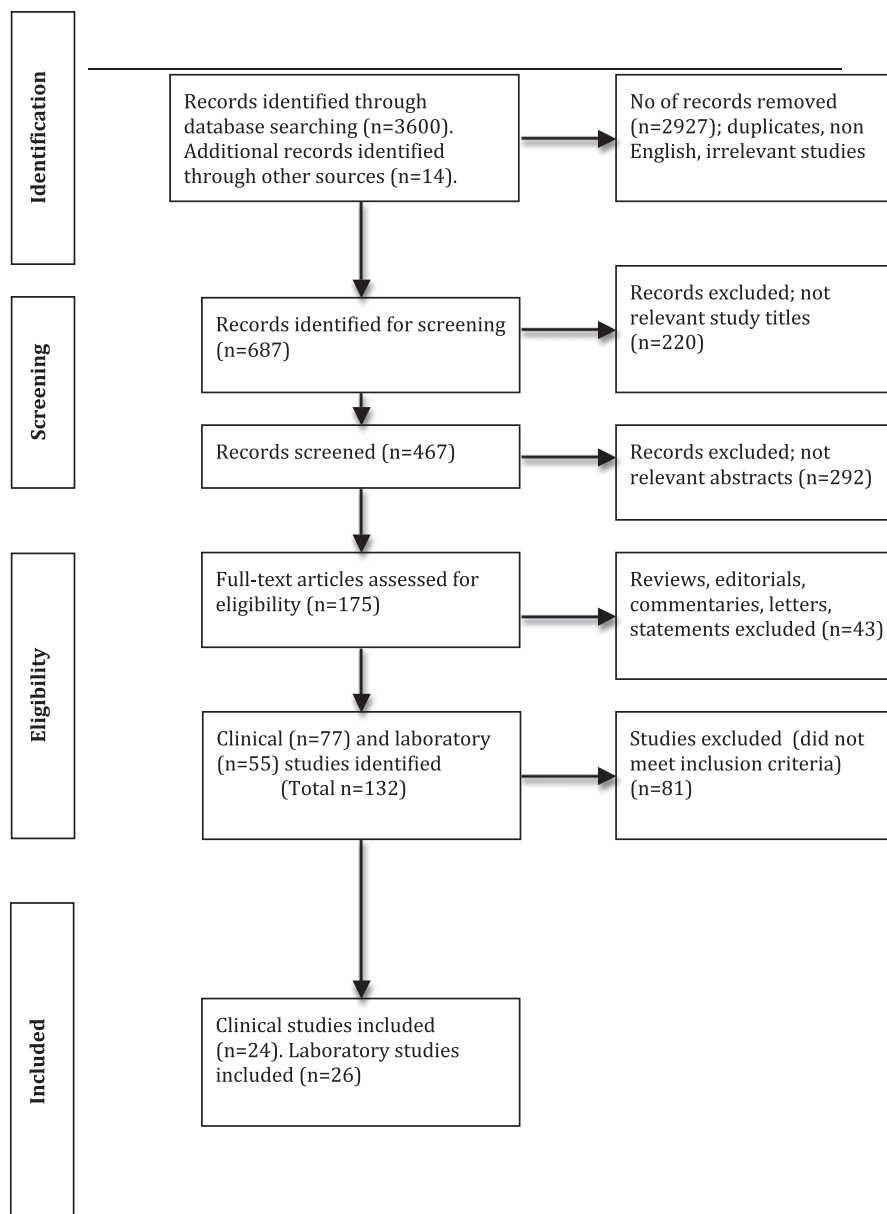

Fig. 2
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram showing the article selection methodology.

and the *Journal of Shoulder and Elbow Surgery*, with the following two sets of search terms: (1) "chondrolysis" AND ("glenohumeral" OR "shoulder"), and (2) "chondrocytes" AND ("local anesthetics" OR "lidocaine" OR "bupivacaine") (Fig. 2). We also searched the bibliography of each of the identified articles for other relevant references. Articles were included if they provided original data on clinical cases of glenohumeral chondrolysis due to any cause or if they provided data on the effect of local anesthetics on cartilage. We excluded editorials, letters to the editor, reviews, and statements of opinion. We also excluded reports of cases that did not meet the generally accepted definition of chondrolysis, which is the generalized destruction of previously normal-appearing glenohumeral joint surfaces. In two instances, we contacted the authors to confirm our understanding of the published data[18,28].

For each clinical study, we recorded the author, year, number of cases of chondrolysis, patient age, patient sex, time between the index procedure and the chondrolysis, use of suture anchors, use of thermal devices, injections of dyes or chlorhexidine, and use and specifics of pain pump infusions (type of local anesthetic, concentration, flow rate, pump volume, and anatomic location). For each laboratory study, we recorded the author, year, experimental model system, type of local anesthetic, concentration, duration of application, time of analysis after anesthetic application, and results. Although our primary approach was to seek evidence in support of the Hill criteria, we also utilized the Fisher exact test and t statistics when applicable.

Results

Reports of 213 cases of chondrolysis were identified. The mean age of the patients was thirty years. The typical findings included documentation of normal-appearing cartilage at the index procedure and a period of benign recovery followed in a few months by the onset of pain and stiffness associated with global loss of articular cartilage from the humeral and glenoid surfaces without prominent osteophytes or evidence of infection. The data from each clinical and laboratory study are summarized in the Appendix.

Glenohumeral chondrolysis was rare before the use of intra-articular pain pumps for the infusion of local anesthetic; the total number of reported cases has increased dramatically since the introduction of the pain pump. Although the early 1990s saw the introduction of suture anchors for labral repair[48] and the use of thermal energy in the management of glenohumeral instability[49-51], published reports of glenohumeral chondrolysis remained rare until a decade later, after the introduction of pain pumps for the intra-articular infusion of local anesthetic following arthroscopic shoulder surgery in the early 2000s (Fig. 3)[52-54]. To our knowledge, the first documented case of chondrolysis in a shoulder receiving pain pump treatment was published in 2004[22]. Subsequently, the number of reported cases of chondrolysis increased rapidly; we identified only six reported cases prior to that report but 204 reported cases after it, and 168 (82%) of the subsequent cases were in shoulders treated with an intra-articular pain pump. Concurrently, chondrolysis following the intra-articular infusion of local anesthetic via a pain pump has also been reported in the ankle[55] and the knee[56-58]. In 2010, a review of the 100 previously published reports of glenohumeral chondrolysis indicated that 59% (fifty-nine) were in shoulders that had received infusion of local anesthetic via a pain pump catheter[26]. Two years later, our present analysis of all published cases revealed that the total number of reported shoulders with glenohumeral chondrolysis had more than doubled (to 213) and the percentage occurring in shoulders that had received local anesthetic via a pain pump catheter has increased from 59% to 79% (169) (Fig. 3).
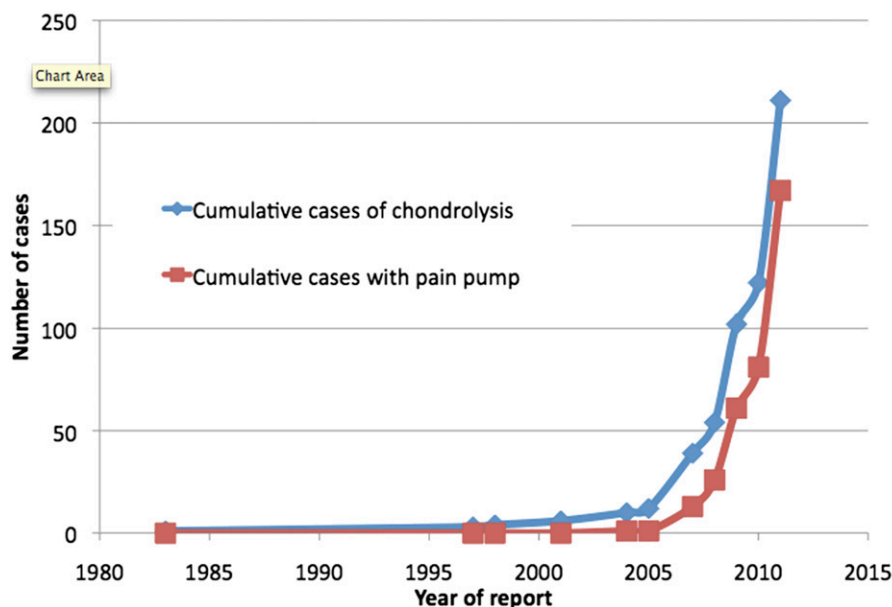
Fig. 3

The cumulative number of published shoulder chondrolysis cases and cases in which a pain pump was used according to year. Suture anchors for labral repair and thermal capsulorrhaphy were introduced in the early 1990s; the use of pain pumps for the infusion of local anesthetic was introduced in the early 2000s. To our knowledge, the first published case of chondrolysis in a shoulder receiving an infusion of local anesthetic via a pain pump was in 2004.

In series of shoulder arthroscopies that included procedures performed with and without use of an intra-articular pain pump, chondrolysis was significantly more common when a pump was used. In a Level-II study, forty-nine of the 109 shoulders in which pain pumps had been used developed chondrolysis, whereas chondrolysis did not occur in any of the 266 shoulders that did not receive intra-articular local anesthetic via a pain pump (p < 0.0001, Fisher exact test)[28]. In another study of 113 shoulder arthroscopies performed by two experienced shoulder surgeons, chondrolysis developed in nineteen of the forty-five shoulders that received intra-articular infusion of local anesthetic via a pain pump but in none of the sixty-eight shoulders that did not (p < 0.0001, Fisher exact test)[15]. In a third report of thirty arthroscopic stabilizations performed by a single surgeon, chondrolysis developed in twelve of the nineteen shoulders that were treated with an intra-articular pain pump catheter but in none of the eleven shoulders that did not (p < 0.0006, Fisher exact test)[17]. Finally, a patient who underwent identical arthroscopic procedures on both shoulders was reported to have developed chondrolysis on the side on which a properly functioning intra-articular pain pump infused local anesthetic but not on the side on which the pumped local anesthetic leaked out onto the skin rather than going into the glenohumeral joint[24].

Chondrolysis was reported after pain pump use only if the infusion of local anesthetic was directly into the joint and not if the infusion was into an extra-articular location in the shoulder. We identified thirteen articles with 962 reported cases in which a pain pump was used to infuse local anesthetic into the subacromial space, and none of these shoulders was reported to have developed chondrolysis[15,23,52,53,59-67].

Local anesthetics are known to be cytotoxic, and the mechanism of their toxicity has been well defined. As is the case for muscle cells[68-71], cells of the intervertebral disc[72,73], lung fibroblasts[74], and nerve cells[75-78], local anesthetics are toxic to the chondrocytes that maintain the integrity of cartilage[4-8,10,12,13,29-32,34-39,41-44,79]. The cytotoxicity of local anesthetics is related to their fat solubility; thus, bupivacaine is more toxic than lidocaine, which is more toxic than ropivacaine, levobupivacaine, and mepivacaine[6,8,12,13,30,32,35-37,40,79-81].

At least three mechanisms for the cytotoxicity of local anesthetics have been documented. First, local anesthetics can disrupt the cell membrane, causing acute necrosis[4,8,12,37,40,43,69,72,76,82]. Second, they can slow mitochondrial respiration by disrupting the mitochondrial transmembrane potential and uncoupling oxygen consumption from the conversion of ADP to ATP[69,80,82]. Third, they can lead to delayed cell death through alteration in mitochondrial DNA resulting in apoptosis[4,8,10,12,37,40,43,69,72,76,82,83].

The cytotoxic effect of local anesthetics on chondrocytes is further confirmed by the repeated observation that the toxicity is related to the dose of local anesthetic to which the chondrocytes are exposed. Laboratory studies have revealed that longer periods of exposure and higher concentrations of local anesthetics are more toxic to cultured chondrocytes and to cultured cartilage[4,35,42]. This dose-toxicity relationship has been demonstrated

for bupivacaine[4,5,8,12,35,37,40,79], lidocaine[8,10,12,40-42], ropivacaine[79], mepivacaine[12], and levobupivacaine[79].

Clinically, the dose of local anesthetic to which chondrocytes are exposed is related to the concentration of the anesthetic in the infusate, the rate of infusion, the volume of the infusion, and the duration of the infusion[15,17,28]. Increased doses of local anesthetic increase the risk of glenohumeral chondrolysis[15,17,28]. Two clinical studies demonstrated the increased toxic effects of high-flow (4 or 5 mL/hr) compared with low-flow (2 mL/hr) pain pumps[15,23]. Combining the results of these two studies, twenty of forty-eight shoulders receiving high-flow infusions developed chondrolysis, whereas only two of twenty-five shoulders receiving low-flow infusions developed this complication (p = 0.0029, Fisher exact test). The clinical dose-toxicity relationship of local anesthetics was further demonstrated in the study of Wiater et al.[28], in which eleven of twenty-two shoulders receiving 0.5% bupivacaine developed chondrolysis compared with none of the six shoulders receiving 0.25% bupivacaine (p = 0.05, Fisher exact test). Of the twenty-two shoulders infused with 0.5% bupivacaine, the mean pain pump delivered volume was 377 mL in the eleven that developed chondrolysis compared with 187 mL in the eleven that did not (p = 0.003, unpaired t test).

In 108 of the cases of glenohumeral chondrolysis, the pain pump flow rate was documented. A high-flow (≥4 mL/hr) pain pump was used in 100 cases and a low-flow (2 mL/hr) pump was used in only eight. In seventy-two cases of chondrolysis following use of bupivacaine, the concentration and flow rate were both reported. A high-flow pain pump was used in sixty-five of these cases to deliver 0.5% bupivacaine (thirty-four cases) or 0.25% bupivacaine (thirty-one cases). A low-flow pain pump was used in the remaining seven cases to deliver 0.5% bupivacaine (five cases) or 0.25% bupivacaine (two cases). Thirty-six cases of chondrolysis were reported following use of lidocaine, and thirty-five of these involved a high-flow pain pump with 2% lidocaine.

The clinical observation that disruption of the articular cartilage surface (e.g., by insertion of suture anchors through it) increases the risk of chondrolysis in shoulders receiving intra-articular infusion of local anesthetics via a pain pump is consistent with laboratory evidence. Because intra-articularly administered local anesthetics must diffuse through the intercellular matrix of the cartilage to the chondrocytes before they can exert their toxic effects, the superficial layer and an intact intercellular matrix offer protection to the embedded chondrocytes[38]. When the surface layer is intact, the toxic effects of local anesthetics are manifested primarily on the chondrocytes in the superficial layers of the cartilage[7,37]. Chondrocytes cultured in monolayers or in alginate beads are not protected by surrounding intercellular matrix and are therefore more susceptible to lower doses of local anesthetics than chondrocytes embedded within intact cartilage[4-7,13,37,42]. When the superficial layer of cartilage is damaged, local anesthetics can more easily reach the chondrocytes within the matrix[4,5,13,42,44]. An intact superficial layer is less able to protect chondrocytes from the toxic effects of lidocaine, which
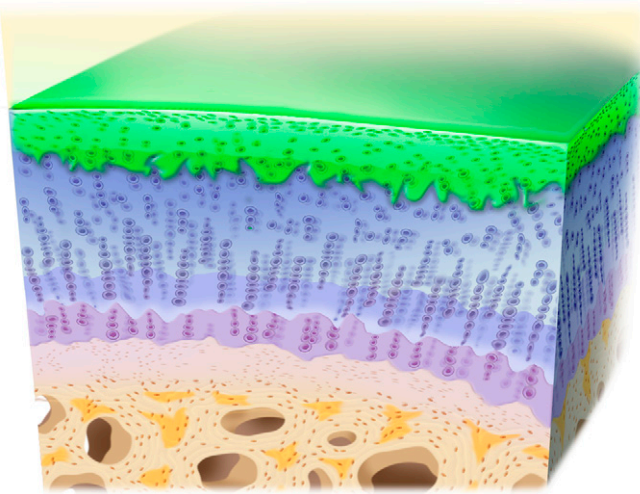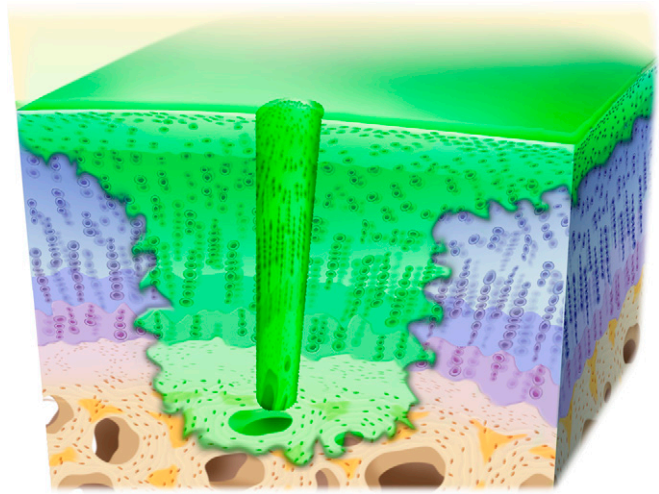
Fig. 4-A

Fig. 4-B

Figs. 4-A and 4-B Diagrammatic cross-sections of articular cartilage exposed to molecules of an anesthetic agent. **Fig. 4-A** Diffusion of local anesthetic through an intact chondral surface. **Fig. 4-B** Facilitated diffusion where the chondral surface is breached.

diffuses more easily through the matrix because of its smaller molecular weight[42].

The integrity of the superficial layer of cartilage may be breached by drilling and insertion of suture anchors during labral repair. Although suture anchors are commonly used for labral and other shoulder repairs, only six of the 213 reported cases of chondrolysis involved use of suture anchors without pain pumps or thermal treatment. In comparison, both suture anchors and an intra-articular pain pump were used in 119 cases of chondrolysis. In an analysis of the procedures performed by an individual surgeon, the risk of chondrolysis in shoulders treated with an intra-articular pain pump was significantly increased if the surgical procedure included the placement of one or more suture anchors in the glenoid (hazard ratio, 2.60 [95% confidence interval, 1.54 to 4.39]; $p < 0.001$)[28].

The clinical observation that chondrolysis manifests several months after the infusion of local anesthetic via a pain pump is consistent with the established effects of these agents on articular cartilage. There was a consistent temporal relationship between the onset of chondrolysis and the anesthetic infusion. The earliest times between pain pump infusion of local anesthetic and the onset of symptoms from chondrolysis were two to eight months after the index procedure[15,16,21,23,28,84]. These results are consistent with the laboratory observation that the extracellular matrix of cartilage is not directly affected by local anesthetics[34]. The delay in the onset of symptoms is most likely due to a combination of two factors. First, lack of cartilage maintenance by chondrocytes affected by local anesthetic will have a delayed rather than an immediate effect on the cartilage. Second, in addition to immediate necrosis, another substantial component of the toxic effect of local anesthetic on chondrocytes is alteration of the mitochondrial DNA leading to delayed cell death through apoptosis[4,8,10,12,37,40,43,69,72,76,82,83].

Discussion

Glenohumeral chondrolysis is a serious, irreversible complication of shoulder surgery in young, active individuals. The number of reported cases of this complication is increasing (Fig. 3). Because chondrolysis is untreatable and irreversible, the incidence of glenohumeral joint destruction due to chondrolysis can only be reduced by prevention. Thus, clear identification of its causes and elimination of these causes is necessary to reverse the observed rise in the rate of occurrence.

The published clinical and laboratory data establish beyond reasonable doubt that chondrolysis is caused by the intra-articular infusion of local anesthetics. A 2010 review of all 100 previously published cases of glenohumeral chondrolysis revealed that fifty-nine (59%) were in shoulders that had received an intra-articular infusion of local anesthetic via a pain pump[26]. Since that review, the number of cases of glenohumeral chondrolysis has more than doubled (to 213). Of the 113 cases reported since the 2010 review, 110 (97%) have been in shoulders that had received an intra-articular infusion of local anesthetic via a pain pump. The risk of glenohumeral chondrolysis in shoulders receiving an intra-articular infusion of local anesthetic was greatest with high anesthetic doses, especially 0.5% bupivacaine or 2% lidocaine infused at a rate of 4 or 5 mL/hr for forty-eight hours or more. These high intra-articular doses of local anesthetic increase the amount of the agent that diffuses through intact cartilage matrix to the chondrocytes embedded in the matrix (Fig. 4-A). Suture anchors can compromise the integrity of the cartilage surface, facilitating diffusion of the anesthetic into the substance of the cartilage (Fig. 4-B). The risk of glenohumeral chondrolysis in shoulders receiving an intra-articular infusion of local anesthetic was significantly increased in shoulders in which suture anchors had been placed for labral repair (hazard ratio, 2.6; $p < 0.001$)[28].

The results of this analysis need to be viewed in light of certain limitations. No prospective randomized clinical studies have been carried out to compare pain pump infusion of local anesthetic with pain pump infusion of a control infusate. The present analysis considers only the published cases of glenohumeral chondrolysis and related laboratory data; it is likely that a considerable number of other cases of glenohumeral chondrolysis have occurred but are not available for review because they have not been published. Complete data (e.g., on the duration of catheter use and the flow rate) were not available for some of the studies; more complete data would have improved the quality of the analysis. In spite of these limitations, the available laboratory and clinical data satisfy the nine criteria set forth by Hill[47] for the demonstration of causation: (1) the strength of the association—the evidence supporting the toxic effect of local anesthetics on chondrocytes is statistically robust; (2) the consistency of the observed association—the link between chondrocyte toxicity resulting in cartilage destruction and local anesthetics has been demonstrated by multiple observers in both the laboratory and the clinical setting; (3) the specificity of the association—the mechanism of the toxic effects of local anesthetics on chondrocytes is well defined; (4) the temporal relationship of the association—there is a consistent chronologic relationship between the exposure of cartilage to local anesthetics and the development of chondrolysis; (5) the existence of a biological gradient—the dose-response relationship between local anesthetics and cartilage toxicity is well documented in laboratory and clinical studies; (6) biological plausibility—the mechanism by which local anesthetics cause chondrolysis is consistent with the current understanding of mechanisms of cytotoxicity; (7) coherence—the cause-and-effect interpretation of the data does not conflict with the generally known facts of the natural history and biology of chondrolysis; (8) experimental evidence—numerous carefully controlled experiments have been performed by multiple investigators demonstrating the dose-related toxic effects of local anesthetics on isolated cells and cartilage tissue; and (9) analogy—the toxic effects of local anesthetics on chondrocytes are analogous to the effects of other toxins, such as chlorhexidine and gentian violet, and the ability of local anesthetics infused via a pain pump to cause glenohumeral chondrolysis is analogous to the chondrolytic effect of such infusions in other joints[55-58].

In conclusion, the existing evidence is sufficient to conclude that the intra-articular infusion of local anesthetic via a pain pump is the principal cause of the cases of glenohumeral chondrolysis reported since 2004. Avoiding the use of intra-articular pain pumps can largely eliminate this complication in orthopaedic surgery.

Appendix

Tables summarizing the data from each clinical and laboratory study are available with the online version of this article as a data supplement at jbjs.org. ■

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OF GLENOHUMERAL CHONDROLYSIS

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