


ORIGINAL ARTICLE

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# Chemical septoplasty using papain enzyme—a feasibility study

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## Abstract

**Background:** Though surgery can correct nasal septal defects through a procedure called septoplasty, many people seek non-surgical options. Papain enzyme has been used in the past to lyse intervertebral disc and has shown to have a lytic effect on cartilage. Therefore, in this paper, the feasibility to use papain for septoplasty was studied.

First, an in vitro study on chicken cartilage was done. Cartilage pieces were emerged in papain solution (5 mg/ml of papain in normal saline) and plain normal saline solution (as control) for 2 weeks at room and refrigeration temperatures. Then, the papain solution was injected in a formalin-fixed cadaver in the submucosal space around the nasal septal cartilage. The control group was injected with normal saline.

**Results:** The treated group showed significant lysis with the disintegration of the cartilage, both in the in vitro and cadaver study.

**Conclusion:** This study shows that papain can lyse cartilage. It also shows that submucosal injection of papain around nasal cartilage will lyse the septal cartilage. Based on prior experience with papain for disc herniation and the present study, it is worthwhile to further investigate this procedure using live animals.

**Keywords:** Cartilage, Nasal septum, Septoplasty, Papain, Chemical septoplasty

## Background

Deviated septum involves the anterior cartilaginous part of the septum. It can lead to cosmetic issues, breathing difficulty, apnea, snoring, facial pain, dryness of the nasal passage, and sinus infections. When medical treatment fails to alleviate the symptoms, the surgical procedure of septoplasty is often considered. The deformity may involve the anterior part of the cartilaginous septum or the entire cartilage. The procedure consists of excision of the cartilaginous portion of the septum to widen the nasal passages to improve airflow [1, 2]. Though this procedure is well tolerated and relatively simple, it has a share of failures and associated complications. Adverse outcomes include nasal adhesions, hematoma formation, and septal perforation. A systemic review compared the

outcomes of eleven studies involving investigations on the effectiveness of septoplasty with concurrent turbinate surgery to septoplasty alone [1]. These studies failed to confirm the effectiveness of septoplasty, and the limitations included failure of studies comparing septoplasty to non-surgical interventions. Furthermore, there are many patients who refuse surgery and continue to suffer from the condition because they are afraid about surgery.

## The aim of the studies

(1) To determine the effect of papain under two different temperature settings, study time duration for cartilage lysis, and to determine the days of treatment needed for lysis to occur. (2) To determine if it was feasible to do chemical septoplasty via needle injection of papain enzyme in the submucosal peri-septal space around the cartilaginous part of the septum.

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### Existing literature

Demonstrated by the work of Thomas [3], the protease known as papain was determined to be effective for the reduction of chondroitin sulfate content within the cartilage matrix. This was evident by the loss of rigidity in rabbit ears following injection of papain. Examination of the cartilaginous tissues from these rabbit ears found a significant portion of the matrix had disappeared; however, a smaller cartilage plate containing relatively normal chondrocytes remained stable in the tissue sample. Based on this, papain has been used in the past in a procedure called chemonucleolysis to lyse lumbar disc herniation [4–7]. Though a small percentage of patients treated with these enzymes experienced anaphylactic reactions [4], the results of the procedure were good. In two meta-analysis studies, the ability of chymopapain to induce chemonucleolysis was determined to be more effective than placebo [5, 6]. Furthermore, fewer surgeries were required in patients who received chymopapain compared to placebo to manage symptoms associated with disc herniation. Potential benefits for seeking non-invasive interventions include reduced iatrogenic injury (e.g., scarring), shorter hospitalization, quicker recovery times, and more cost-effectiveness [7].

### Necessity for this study

The study to determine the number of days needed for cartilage lysis in vitro and the feasibility to the perform procedure.

### Method

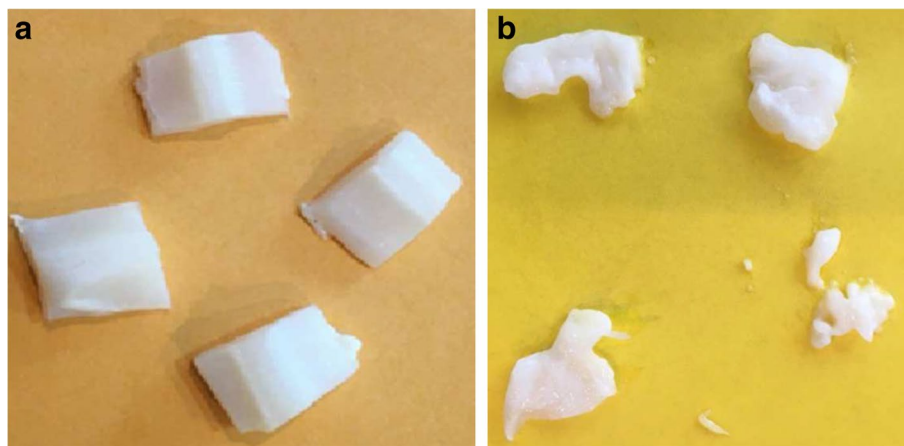
The aim of the design was to study the effect of papain on the cartilage in vitro under two different temperature settings and directly on the cartilaginous part of the nasal septum in formalin-fixed cadavers.

### Study on chicken cartilage (in vitro)

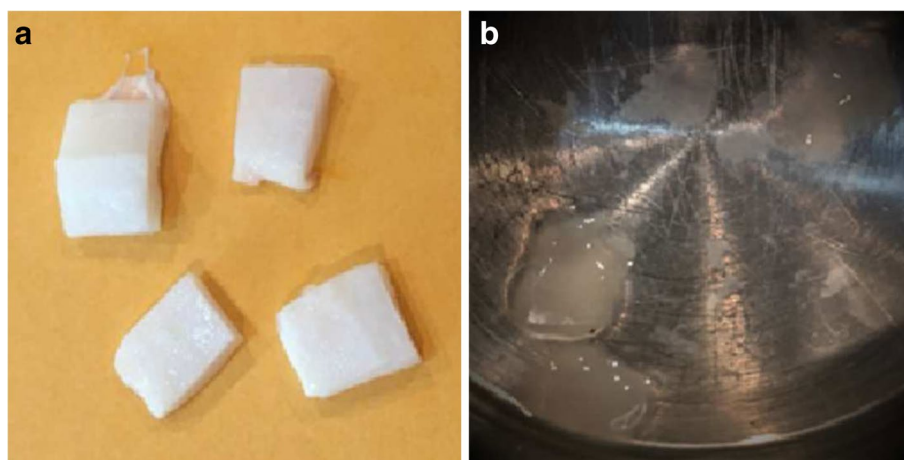
The study was conducted on cartilage pieces measuring 8mm × 8mm × 3mm obtained from fresh chicken breast. They were divided into four groups with four pieces in each group. In group A, the cartilage pieces were immersed at 4°C in a solution containing normal saline for 2 weeks (Fig. 1a). In group B, the cartilage pieces were immersed at 4°C in a solution containing 5mg/ml of papain (Sigma, chemicals, St. Louis, MO) in normal saline for 2 weeks (Fig. 1b). In group C, the cartilage pieces were immersed at 22°C in a solution containing normal saline for 2 weeks (Fig. 2a). In group D, the cartilage pieces were immersed at 22°C in a solution containing 5mg/ml of papain in normal saline for 2 weeks (Fig. 2b). All cartilage pieces were then examined by palpation and visual inspection and were graded on a scale from 1 to 4, where 4 is for the firm and intact, 3 is for soft and intact, 2 is for soft and fragment, and 1 is for gelatinous-semi-liquid or completely gone. During the study, the cartilage pieces were daily observed. When the papain group showed overall disintegration, the study was stopped.

### Cadaver study

Cadaver studies were performed on nine formalin-fixed donors in the anatomy department cadaver laboratory. The cadavers were obtained from the state board of anatomy, which fully consented for their use in education and research. Therefore, IRB approval was not needed. Injections were done using a 25-gauge needle which was inserted into the submucosal space at a 1 ml anterior to the anterior end of the cartilage and then advanced posteriorly by a centimeter. Group A is the control group with four donors which has an injection of 1ml of normal saline in the submucosal space around



**Fig. 1** a Pieces of cartilage treated with normal saline at 4°C for 10 days. b Pieces of cartilage treated with papain in normal saline at 4°C for 10 days



**Fig. 2** **a** Pieces of cartilage treated with normal saline at 22°C for 10 days. **b** Pieces of cartilage treated with papain in normal saline at 22°C for 10 days

the cartilaginous part of the nasal septum. Group B has an injection of papain enzyme in the submucosal space around the cartilaginous part of the nasal septum—5mg in 1 ml of normal saline in one donor and 10mg in 1 ml of saline in four donors. After 14 days, the nasal septums were examined to determine their softness, and after 21 days, the septums were dissected and the cartilaginous part of the septum was examined by palpation and visual inspection. The condition of the septums after treatment was graded on a scale from 1 to 4, where 4 is for the firm and intact, 3 is for soft and intact, 2 is for soft and fragment, and 1 is for gelatinous-semi-liquid or completely gone.

## Results

### In vitro study

The following were the findings after 2 weeks of treatment (Table 1):

*At a temperature of 4°C:* In group A (treated with normal saline), all 4 pieces of cartilage were grade 4. In B (treated with 5 mg papain/ml solution), all 4 pieces were grade 2.

*At a temperature of 22°C:* In group C (treated with normal saline), all 4 pieces were grade 3. In group D (treated with 5 mg papain/ml solution), all 4 pieces were grade 1.

### Cadaver study: papain-treated group (Table 2)

*14 days after treatment:* 4/5 were grade 3 and 1/5 was grade 2.

*21 days after treatment:* 3/5 were grade 1, 1/5 was grade 3, and 1/5 was grade 2.

### Cadaver study: saline-treated group (Table 3)

The cartilages in all 4 donors stayed at grade 4 level for all 21 days.

The average integrity of the septum at 21 days after the injection of papain was found to be 1.6, which is less than the average integrity of the septum at 21 days after injecting the saline.

## Discussion

Lysis of the herniated intervertebral disc using papain enzyme is a well-recognized procedure that was found to be effective in alleviating neurological signs and symptoms of herniated intervertebral disc [4–7].

**Table 1** Integrity of chicken cartilage at 4°C and 22°C (room temperature) after incubation with 5mg/ml papain or saline after 2 weeks

Sample number	Chicken cartilage integrity (grades after 2 weeks)			
	Saline at 4°C: group A	5mg/ml papain at 4°C: group B	Saline at 22°C: group C	5mg/ml papain at 22°C: group D
1	Firm and intact	Fragmented	Soft and intact	Gelatinous-semi-liquid
2	Firm and intact	Fragmented	Soft and intact	Gelatinous-semi-liquid
3	Firm and intact	Fragmented	Soft and intact	Gelatinous-semi-liquid
4	Firm and intact	Fragmented	Soft and intact	Gelatinous-semi-liquid

**Table 2** The data in the cadaver study in which donors received an injection of papain around the cartilaginous part of the nasal septum

Donor number: submucosal injection of xx mg—papain in 1 ml normal saline around the cartilaginous septums	Grades 14 days after injection	Grades after dissection—21 days after injection (upon palpation and inspection)
Donor 1, 5 mg papain	3	3
Donor 2, 10 mg papain	2	1
Donor 3, 10 mg papain	3	1
Donor 4, 10 mg papain	3	2
Donor 5, 10 mg papain	3	1

**Table 3** Results in the control group (saline injection)

Donor number: submucosal injection of normal saline around the cartilaginous septums (group B)	Grades 14 days after injection	Grades after dissection—21 days after injection (based on palpation and inspection)
Donor 1, 1 ml normal saline	4	4
Donor 2, 1 ml normal saline	4	4
Donor 3, 1 ml normal saline	4	4
Donor 4, 1 ml normal saline	4	4

Although this procedure was fairly safe and effective, it was abandoned because there were reports of neurological complications [8] and there was concern about anaphylaxis [4]. It has been reported that the prevalence of allergic reactions to chymopapain is between 0.5 and 0.7%. The risk of anaphylaxis can be mitigated by performing a skin allergy test and IgE antibody tests [8]. The neurological complication was understandable given the procedure's proximity to the neural axis. This should not be a problem for chemical septoplasty procedures. The problem of anaphylactic reaction was well handled in most centers with preoperative administration of steroids and antihistamines and immediate availability of drugs to counteract it. Furthermore, there is no significant evidence that this enzyme has systemic ill-effect [9]. Furthermore, early studies have also shown that papain softens cartilage. Therefore, the use of this enzyme to lyse cartilage in the nasal septum is logical. Furthermore, since it is an injection procedure, it can always be repeated to improve the outcome.

The first part of the research examined the effects of papain on chicken cartilage using an in vitro model. The study was done at room temperature (22°C) and refrigeration temperature (4°C). When treated with papain at refrigeration temperature, the cartilage

pieces showed a marked reduction in structural integrity. When the chymopapain treatment was studied at room temperature, the chicken cartilage was nearly dissolved. Furthermore, even in the control group, there was an element of softness to the cartilage. This indicates that there was some natural degeneration of the cartilage at room temperature. This information is important if one tries to quantify the lytic property of papain. Although the same, there was a dramatic breakdown of the cartilage compared to the control group at both temperatures. This clearly indicates papain's ability to break down cartilage. The authors could have done a study on a larger number of cartilage pieces. However, because the results were overwhelmingly positive, no further in vitro cartilage studies were done.

Usually, the mucosa is very adherent to the cartilage, especially when it is formalin fixed. Therefore, the needle insertion point was therefore 1 ml anterior to the anterior end of the cartilage. In five donors that had papain injection, disintegration of the nasal septal cartilage was observed at two. On further follow-up, at 3 weeks, the average integrity of the septum at 21 days was found to be 1.6 (gelatinous), which is less than the average integrity of the septum 2.8 (soft) at 14 days. This shows progressive disintegration over several weeks.

In the in vitro study, a similar pattern of lysis was seen. Generally, it is known that formaldehyde inhibits the action of papain [10]. However, since cartilage do not have blood vessels in them, it is possible that formalin infused through the vascular system does not reach the inside of the cartilage. This might explain why there was lysis of the cartilage in this study. Furthermore, there was a distinct difference between the control group and the treated group.

In a previous clinical report on the use of papain for disc herniation, 6–8 mg of papain were injected per disc space [11]. Therefore, in the current study, the authors used dosages in the same range. In the cadaver study, the authors found 10mg of papain in a 1-ml solution adequate for septolysis. In clinical use, therefore, a similar dosage could be injected. However, if the entire deformity is not covered with papain solution, additional milliliters of the solution could be injected. The area covered by the solution can be determined by observing the elevation of the mucosa after injection. Additionally, if deformity has not completely lysed after a month, an additional injection could be done.

There are concerns about using papain because of reports of allergic and neurological complications associated with its use in treating disc herniation. The risk of neurological complication in disc disease treatment is due to its close proximity to the thecal sac. This risk is not likely to happen with a submucosal injection around the nasal septum. Another concern is about allergic reaction to papain. This has been discussed in the first paragraph of this section. Yet, another concern is about papain getting into the systemic blood circulation during submucosal injection because of the high vascularity of the nasal mucosa. Therefore, care must be taken to prevent direct vascular injection. Fortunately, one of the early studies in live rabbits included intravenous injection of chymopapain. This did not result in systemic ill-effects [9]. There are two mechanisms preventing systemic effects. First, the chymopapain would be rapidly diluted and pose little concern. Second, the chymopapain would be exposed to a pH of 7.4, reducing its effectiveness (optimal pH of chymopapain is 6–7). Chymopapain may also be exposed to non-selective inhibitors in the blood [12].

## Conclusion

Chemical septoplasty is a simple procedure of injecting papain enzyme around the cartilaginous part of the anterior nasal septum to lyse it and relieve nasal obstruction. Based on previous clinical experience with this enzyme in disc disease, this procedure may be an option for patients who are not suitable for the surgical procedure because

of their medical condition or their unwillingness to undergo the surgical procedure. Though there will always be concern about allergic reactions, this can be easily mitigated with pre-operative testing and readiness during the procedure to manage an allergic reaction. The present in vitro showed a good lytic effect of the enzyme on the cartilage both in in vitro and in cadaver study. Therefore, further investigation of this procedure using live animals might be worthwhile.

## Acknowledgements

None.

## Authors' contributions

AP is the main author who did all the studies and wrote the paper. DKP did the data analysis and statistical studies. AS is a medical student who helped with the study and also in writing the paper. TN-M is a medical student who helped with the study and also in writing the paper. All authors have read and approved the final manuscript.

## Funding

There was no external funding for this paper.

## Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

## Declarations

### Ethics approval and consent to participate

The cadavers were obtained from the state board of anatomy, which fully consented for their use and that IRB board approval was not required.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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Received: 25 March 2021 Accepted: 30 September 2021

Published online: 21 October 2021

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