RESEARCH ARTICLE

CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2024.2024-43
Cyprus J Med Sci 2024;9(6):444-449

The Effect of Quince Seed Mucilage on Human Foreskin Stem Cell Proliferation and Self-Renewal Potential

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Abstract

BACKGROUND/AIMS: Quince seed mucilage (QSM) is used in Iranian folk medicine to treat wounds and burns. Mucilage is rich in polysaccharides and proteins. Approximately 80% of breastfeeding women experience nipple pain and soreness, often applying homemade QSM to treat nipple cracks. There are limited studies on the cytotoxic effects of QSM on fibroblast formation. The present study investigated the proliferative effects of QSM on mesenchymal stem cells isolated from newborn foreskin (hnFSSCs).

MATERIALS AND METHODS: Following a standard circumcision procedure, cells were isolated and cultured in suitable media to support growth. The quince seed gel was prepared and pulverized by drying. Foreskin stem cells were immunocytochemically characterized using CD45, CD34, and CD90 antibodies. The cytotoxic effect of quince seed gel on hnFSSCs was determined using the MTT assay. The cells were then treated with quince seed gel for 24 h, and immunohistochemical staining for Ki-67, c-Myc, OCT¾, and Sall4 was performed.

RESULTS: Immunohistochemical analysis revealed that hnFSSCs were positive for CD, CD90, and CD45 and weakly positive for CD34. The MTT results showed that quince seed gel treatment at 100 µg/mL for 24 h was the most appropriate concentration and duration compared with the positive control. QSM-treated cells showed significantly higher immunoreactivity for Ki-67 (H-score: 266.5±12.6), OCT¾ (H-score: 239±8), and Sall4 (H-score: 243.8±7.5) in comparison with the control group ($p<0.05$). In contrast, c-Myc (H-score: 226±18.8) immunoreactivity was moderate in both groups, with no significant difference ($p>0.05$).

CONCLUSION: Our results suggest that QSM can support the maintenance of self-renewal and pluripotency properties in human foreskin-derived stem cells.

Keywords: Human foreskin tissue, quince seed mucilage, stem cells, fibroblasts formation, cydonia oblonga miller

INTRODUCTION

Many natural products and plants have healing properties that are beneficial for wound healing. One such herbal product is the quince fruit (Cydonia Oblonga Miller), which belongs to the Rosaceae family. This plant, which originates in Iran, can be found in various regions across the globe. In Iranian traditional medicine, it is commonly used to treat a variety of illnesses. Upon contact with water, the seeds of this plant expand and form a gel-like substance referred to as mucilage. This substance has numerous health benefits due to its antioxidant, anti-ulcerative, antimicrobial, and wound-healing properties. Mucilage is a long-chain mucopolysaccharide. When applied to a wound, it helps

To cite this article: Mammadov B, Mammadov E, Becer E, Vatansever HS. The Effect of Quince Seed Mucilage on Human Foreskin Stem Cell Proliferation and Self-Renewal Potential. Cyprus J Med Sci. 2024;9(6):444-449

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Received: 30.05.2024
Accepted: 07.11.2024

to keep the wound moist and provides the necessary nutrients and environment for the cells involved in the healing process. Additionally, its antimicrobial properties help to prevent infection and promote healing. Quince cell mucilage (QSM) has been widely investigated in the last decade as a biological scaffold for tissue engineering and as a wound healing agent.[1-5]

Mesenchymal stem cells, which are versatile progenitor cells capable of self-renewal, can be extracted from various sources like adipose tissue, dental pulp, placenta, and newborn human foreskin tissue (NHF). These cells possess the remarkable capacity to transform into fat, bone, and cartilage, with only a limited number required to generate each of these tissue types.[6,7] Mesenchymal stem cells are preferred for the treatment of numerous conditions, including orthopedic injuries, autoimmune diseases, and liver problems.[8] Additionally, these cells can differentiate into different types, such as fibroblasts, which are integral components of various bodily tissues like skin, nerves, and muscles. Fibroblasts play a considerable role in the healing of skin wounds and have important implications for regenerative medicine.[9]

NHF, which is typically discarded waste, serves as a source of mesenchymal stem cells. This tissue is a skin part that develops beneath the glans penis during the third month of intrauterine life. Notably, it has the capability to proliferate without undergoing cell differentiation for an extended period after birth and can be acquired during neonatal circumcision procedure.[10] The interaction of QSM with different types of cells, such as fibroblasts, keratinocytes, and adipose-derived stem cells, has been demonstrated to be biocompatible and not cytotoxic.[5,11,12] To the best of our knowledge, the impact of QSM on foreskin-derived stem cells remains unexplored. In this study, we aimed to interpret the cytotoxic and proliferative impacts of QSM on human foreskin-isolated stem cells. In addition, human foreskin-isolated cells were characterized.

MATERIALS AND METHODS

Stem Cell Isolation and Culture from Human Foreskin Tissue

The assay was designed as an *in vitro* cell culture study. NHF tissues were obtained from two patients aged 20 and 25 days during a routine newborn circumcision procedure at the university hospital. Written informed consent was obtained from the patients' parents before surgery. The Institutional Ethics Committee granted approval for the study, ensuring adherence to ethical standards [Near East University, Ethics Committee of Health Sciences (approval number: YDU/2018/62-658, date: 18.10.2018)]. The foreskin tissue's mucosal part was separated from the specimen and digested with collagenase type 1 enzyme (Sigma, C0130) for 1.5 h at 37 °C. Thereafter, cells were centrifuged and seeded in 6-well plates. The cells were grown in DMEM-F12 medium supplemented with 1% antibiotics (penicillin-streptomycin), 10% fetal bovine serum (FBS) (Capricorn Scientific, FBS-11B), and 25 µg/mL amphotericin B (Gibco, 15290018) in a humidified incubator at 37 °C and 5% CO_2. When the cells reached an 80-85% confluent, they were passage usage trypsin-EDTA solution (0.25%, Biochrom, L 2143). The cultured cells from passage three were used in all experiments.

Human Foreskin Stem Cell Characterization

Stem cells from NHF tissues were characterized using the protocol our study group previously described.[13] Cells were fixed and incubated with primary antibodies prepared in phosphate-buffered saline (PBS). Specification of the cell characteristics, primary antibodies against CD90 (Thy-1 glycoprotein, Santa Cruz, sc-19614), CD45 (Santa Cruz, sc-1178), and CD34 (Santa Cruz, sc-74499) were used. The biotinylated secondary antibody and enzyme-labeled streptavidin (Thermo, TP-060-HL) were added and incubated. Then, cells were stained with diaminobenzidine (DAB, ScyTek Laboratories ACK125) for 4 min for immunolabeling. The following washing with water, the cells were counterstained with Mayer's hematoxylin (Bio Optica 1213) for 3 min. All staining specimens were examined under a light microscope (Olympus BX40, Tokyo, Japan).

Preparation of Quince Cell Mucilage

First, we separated the seeds from the fresh pulp. The seeds were then dried in a shaded area, maintaining a temperature of 25-30 °C. 50 grams of quince seeds were added to 1000 mL of distilled water. Heat to 50-60 °C and mix for 30 min to extract the mucilage. After allowing the beaker containing quince mucilage to sit for 30 minutes, it was allowed to reach a temperature of nearly 40 °C, ensuring that the conditions were conducive for further processing. Following this step, the mixture was delicately filtered using a clean linen cloth, allowing for the careful separation of the mucilage. The QSM was carefully heated in an oven at 40 °C to obtain a pure dry powder. From 100 g of mucilage, we successfully extracted 9.86 g of this valuable dried powder, demonstrating the efficiency of our process.

Cell Viability and Cytotoxicity Assessment

3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) was used to assess the cytotoxic effects of QSM. The MTT assay was performed in accordance with the study of Becer et al.[14]. PBS was used for QSM powder dissolution. Then, it was diluted with the culture medium at five different concentrations (25, 50, 100, 200, 400 µg/mL). The cells of NHF were suspended in culture medium and seeded in 96-well culture plates at a density of 5×10^3 in each well with 100 µL of the medium. The cells were incubated with five different concentrations of QSM during both hours (24 and 48). Thereafter, 10 µL MTT solution was added to each well, and the mixture was incubated at 37 °C for 4 h. Thereafter, dimethyl sulfoxide (DMSO, Sigma, D2650-5X5ML) at a volume of 50 µL was added for dissolving the formazan salts. The absorbance values were measured at 540 nm (Versa Max, Molecular Device, Sunnyvale, USA). All MTT tests were done in 3 times.

Immunocytochemical Evaluation

The indirect immunoperoxidase method was used to evaluate Ki-67, myc, OCT¾, and Sall4 protein distributions after quince seed gel administration as previously described.[15] 5×10^3 cells/well were seeded into 24-well plates and incubated with quince seed gel for 24 h. Thereafter, cells of NHF were fixed with 4% paraformaldehyde (158,127-25G, Sigma-Aldrich) for 30 min and washed twice with PBS. In addition, cells were permeabilized using 0.1% Triton-X 100 (Merck, 108603) for 15 min. Then, 3% H_2O_2 (Sigma-Aldrich, 7722-84-1) was added for 11 min, and blocking solution was added for 10 min. Primary antibodies against Ki-67 (Thermofisher Scientific, RB-081-A1), c-Myc (Invitrogen, 14-6784-82), OCT¾ (Invitrogen, 12-5841-82), and Sall4 (Abcam, ab57577) were added and incubated overnight at +4 °C. Then, they were washed with PBS and treated with biotinylated secondary antibodies and enzyme-labeled streptavidin (TP-060-HL/Thermo) for 5 min. After washing with PBS, DAB chromogen was added, and cells were incubated for 3 min. After washing through distilled water, counterstaining was applied with Mayer's hematoxylin for 4 min. Staining intensities of Ki-67, c-Myc, OCT¾, and Sall4 were graded semi-quantitatively using H-score. The

H-score = Σл (i+1) equation was used. In addition, "i" in the equation indicates the staining intensity and is graded as 3, strong; 2, moderate; and 1, weak. The symbol "л" indicates the percentage of cells stained at various intensities, with values ranging from 0% to 100%. This metric is crucial for quantifying staining intensity.

Statistical Analysis

The data were presented as mean ± standard deviation. Additionally, the GraphPad Prism 7 program was utilized in the analysis, and group differences were analyzed using the Mann-Whitney U tests. P<0.05 was considered statistically significant.

RESULTS

MTT Evaluation

NHF cells were treated with five different concentrations (25, 50, 100, 200, and 400 µg/mL) of QSM for 24 and 48 h. We found that 100 µg/mL of QSM was more effective for cell viability protection at 48 h in cells (Figure 1). According to the cell viability results, the QSM protected the cell viability owing to its cell growth and repair-promoting effect.

Cell Morphology

Spindle shape and fibroblast-like morphology of foreskin-isolated stem cells were observed in both quince seed gel-treated and control cells (Figure 2A, B). The number and morphology of NHF cells did not differ after the application of quince seed gel.

Immunocytochemical Evaluation

The immunoreactivities of Ki-67 were strong in QSM-treated NHF cells (Figure 3A), and the staining intensity was significantly higher than that of the control group of NHF cells (Figure 3B) (p<0.05, Table 1). Moderate immunoreactivity of c-Myc was detected in both QSM-treated (Figure 3C) and control (Figure 3D) cells. However, the results showed no significant difference in c-Myc immunoreactivity compared with the control group (p>0.05, Table 1). The OCT¾ immunoreactivity was strong in QSM-treated NHF cells (Figure 3E), and the staining intensity was statistically significant compared with the control group of NHF cells (Figure 3F) (p<0.05, Table 1). Strong and weak Sall4 immunoreactivities were defined in the QSM and control groups, respectively (Figure 3G, H). The Sall4 H-score value in the NHF cells was considerably different from that in the control group (p<0.05, Table 1).

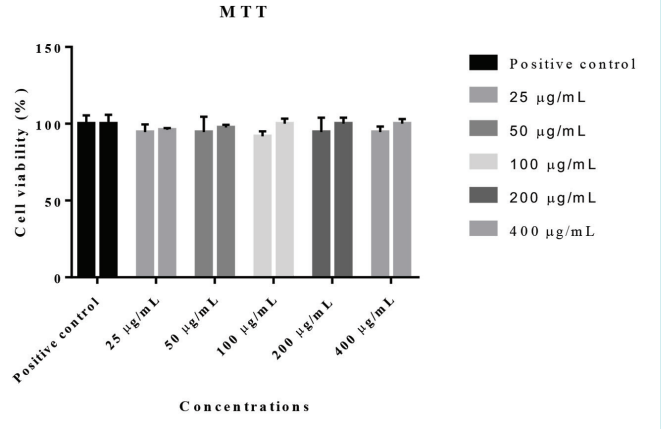

Figure 1. Effect of QSM on cell viability of cells. Cells were treated with five different concentrations of quince seed gel for both hours (24 or 48). Absorbance = 540 nm.

DISCUSSION

Quince, a fruit predominantly cultivated in Iran, Türkiye, and the Caucasus region, is well-known for its healing properties in this region. Quince seeds are used to treat diarrhea, cough, and intestinal colic as part of folk medicine practice. When seeds are placed in water, a colloidal solution, called mucilage, is formed from the seed cores. In particular, quince seed mucilage (QSM), which is abundant in healing attributes, is often used to treat nipple cracks in breastfeeding mothers in Türkiye. Extensive research has focused on QSM, and its chemical composition has revealed a structure primarily comprised of water-soluble polysaccharides such as methoxyuronic acid and cellulose. Subsequent studies identified the chief water-soluble polysaccharide within QSM as a partially O-acetylated (4-O-methyl-D-glucurono)-D-xylan containing a notable concentration of glucuronic acid residues. Moreover, acid hydrolysis showed that the mucilage consists of L-arabinose, D-xylose, and aldobiuronic acid.[3,16,17] The QSM has two applications as a tissue engineering substrate for scaffolds and wound-healing materials. A study by Jafari et al.[12] demonstrated that QSM/polyvinyl alcohol scaffolds exhibited strong fibroblast adhesion along with exceptional biocompatibility. Şimşek et al.[18] developed bioengineered three-dimensional constructs from QSM, showing strong attachment and migration of human adipose-derived mesenchymal stem cells, with no cytotoxicity observed. The researchers concluded that QSM has the potency to be a substitute for routinely utilized polysaccharides in tissue engineering and regenerative medicine studies.[18] In another application, Cetin Genc et al.[19] enriched QSM with nano-hydroxyapatite, manufactured scaffolds by freeze drying, and analyzed the osteogenic derivation of human adipose-stem cells from mesenchymal tissue. Immunohistochemical staining indicated that cells with a spherical morphology infiltrated the bioscaffold pores, whereas real-time polymerase chain reaction analyses showed an early up-regulation of osteogenic markers. The authors believe that QSM scaffolds enriched with nanohydroxyapatites have the potential for regenerative applications, especially in non-load bearing areas, such as the craniomaxillofacial region.[19]

QSM has also been researched as a material to promote wound healing. Hemmati et al.[20] investigated the impact of QSM cream on the T-2 toxin-induced dermal toxicity in rabbits and showed significant healing changes compared with the untreated and sham groups. Tamri et al.[21] demonstrated that 20% cream produced from QSM at the Eucerin base showed increased growth factors (EGF; TGF-β1; VEGF; PDGF) in the wound fluid. In addition, wound contraction was faster and the tensile strength of the wound was enhanced in the wound treated with 10% and 20% QSM cream compared with the control group. Furthermore,

Table 1. H-score values of Ki-67, c-Myc, OCT¾, and Sall4 in cells treated with QSM at 100 µg/mL QSM for 48 h and control group

	QSM group	Control group
Ki-67	266.5±12.6*	103.8±4.8
c-Myc	226±18.8	211±3.4
OCT¾	239±8*	107.5±9.5
Sall4	243.8±7.5*	105±5.8

*The data were significant compared with the control group (p<0.05). QSM: Quince seed mucilage.

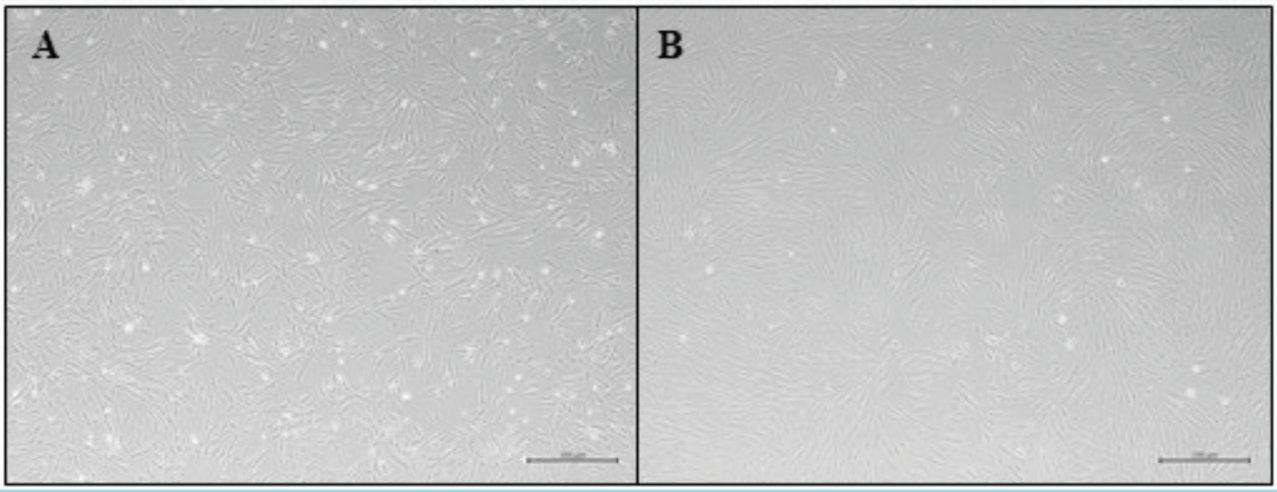

Figure 2. Cells were viewed under an inverted microscope after treatment with control (A) gel or quince seed gel (B). Scale bar = 200 µm.

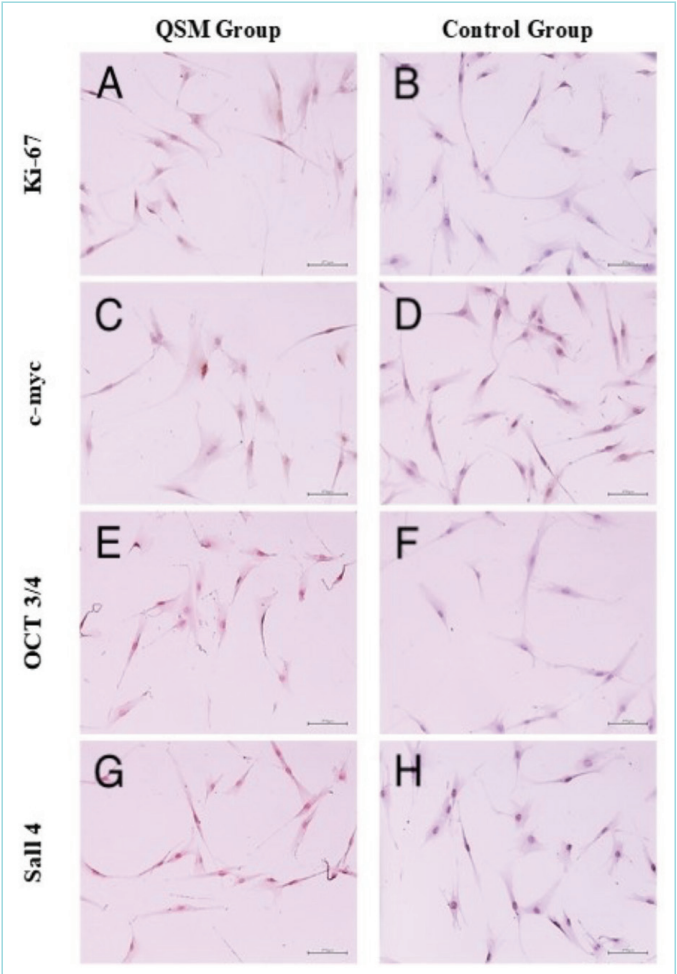

Figure 3. Immunoreactivity of Ki-67 (A, B), c-Myc (C, D), OCT¾ (E, F), and Sall4 (G, H) in cells after treatment with 100 µg/mL QSM (A-G) and control (B-H) groups. Scale bar = 200 µm.

Xin et al.[22] demonstrated that a conditioned medium derived from human foreskin-isolated cells, when combined with hyaluronic acid, promotes the regeneration of the extracellular matrix and accelerates wound healing in diabetic mice.

Recent research has revealed that cells isolated from the human foreskin exhibit fibroblast-like structures and possess stem cell properties, as well as pluripotent and multipotent abilities.[13,23] Additionally, human foreskin-isolated cells have become commercially available and are used in products like Apligraf® (Organogenesis, Inc.) and Dermagraft® (Organogenesis, Inc.).

In this study, we conducted experiments to assess the impact of QSM on human foreskin-isolated stem cells. Specifically, we investigated the influence of QSM on the proliferation and stem cell properties of these cells. Notably, our study represents the first study to examine the impacts of QSM on the proliferation and activation of stemness signaling pathways in human foreskin-isolated cells. To explore this, we exposed human foreskin-isolated cells to various concentrations of QSM (25-50-100-200-400 µg/mL) for 24 and 48 h. We evaluated cell viability using the MTT assay and found that all concentrations were non-toxic, indicating that the selected concentration and time frame enhanced cell viability. Our results showed that 100 µg/mL of QSM was particularly effective at enhancing cell viability after 48 h of exposure.

Ki-67, a nuclear protein, is used as a marker to determine proliferating cells. According to the results of our study, the immunoreactivity of Ki-67 was crucially higher in QSM-treated human foreskin-isolated cells than in the control group. Ghafourian et al.[24] reported that QSM stimulated human skin fibroblast proliferation. QSM could be used as a wound-healing agent. Quince seeds contain phenolic compounds (3,5-caffeoylquinic acids, caffeoylquinic,…), amino acids (asparagine, glutamic and aspartic acids), and organic acids (ascorbic, citric, malic, fumaric acids, ...).[25] The rich phytochemical profile of quince seeds indicates the proliferative effects and wound-healing activities of QSM.

Sall4 (Spalt-like transcription factors 4) is a transcription factor essential for the self-renewal and pluripotency maintenance of stem cells. Sall4 protein expression gradually reduces with the tissues and organs maturation.[26] It regulates transcription key stemness factors, such

as OCT¾, SOX2, and c-Myc. OCT¾ and c-Myc are especially important regulators for maintaining the self-renewal and pluripotency of stem cells.[27] Our results showed that Sall4 and OCT¾immunoreactivities were significantly higher in QSM-treated human foreskin-isolated cells compared with the control group. Moreover, c-Myc immunoreactivity was higher in QSM-treated human foreskin-isolated cells than in control cells. Although a difference was observed between the groups, the difference did not reach statistical significance.

Study Limitations

The chemical composition of QSM can vary depending on the source and preparation method. Standardizing the extraction and preparation processes will ensure consistency and reproducibility in future research. Our study was conducted *in vitro*. To confirm the applicability of our findings, additional studies must be conducted using relevant *in vivo* models and eventually human trials.

CONCLUSION

Our findings demonstrate that QSM at a concentration of 100 µg/mL significantly enhances cell viability and promotes the expression of key stemness factors, such as Sall4 and OCT¾, in human foreskin-isolated stem cells. These outcomes suggest that QSM can support the maintenance of self-renewal and pluripotency properties in these cells. Further studies are required to identify the mechanisms underlying the effects of QSM on stem cell proliferation and activation pathways to harness its therapeutic potential in regenerative medicine.

MAIN POINTS

- **Effective Concentration:** The 100 µg/mL concentration of QSM significantly enhanced cell viability after 48 h, indicating its potential for cell growth and repair.
- **Morphology Consistency:** Treatment with quince seed gel did not alter the spindle shape or fibroblast-like morphology of foreskin-isolated stem cells, maintaining the number and form of cells.
- **Immunoreactivity Increase:** QSM treatment resulted in a marked increase in Ki-67 and OCT¾ immunoreactivity, with statistically significant differences compared with the control group, whereas c-Myc showed no significant change.

ETHICS

Ethics Committee Approval: The Institutional Ethics Committee granted approval for the study, ensuring adherence to ethical standards [Near East University, Ethics Committee of Health Sciences (approval number: YDU/2018/62-658, date:18.10.2018)].

Informed Consent: Written informed consent was obtained from the patients' parents before surgery.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.M., Concept: B.M., E.M., E.B., H.S.V., Design: B.M., E.M., E.B., H.S.V., Data Collection and/or Processing: B.M., E.M., E.B., H.S.V., Analysis and/or Interpretation: E.M., H.S.V., Literature Search: B.M., E.M., E.B., H.S.V., Writing: B.M., E.M., E.B., H.S.V.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study had received no financial support.

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