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Volume-Stable Collagen Matrix as a Recombinant Human Bone Morphogenetic Protein-2 Carrier for Maxillary Sinus Augmentation: An Experimental In Vivo Study

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ABSTRACT

Aim: To test the hypothesis that a volume-stable collagen matrix (VCMX) can serve as an effective rhBMP-2 carrier for bone regeneration while compensating for the volume instability of absorbable collagen sponge (ACS).

Materials and Methods: (i) rhBMP-2 release kinetics from VCMX and ACS were measured over 7 days by enzyme-linked immunosorbent assay. (ii) Bilateral sinus augmentations were performed in 15 rabbits using either VCMX or ACS, with or without rhBMP-2. After 4 weeks, radiographic and histological analyses were conducted.

Results: The overall release patterns between VCMX and ACS did not differ significantly, although VCMX showed a delayed peak release (at 3 h) compared to ACS (at 10 min). Three-dimensional radiographic analysis showed greater volumetric gains in VCMX groups than in ACS groups, regardless of rhBMP-2 loading. Histologically, VCMX/rhBMP-2 group exhibited the largest total augmented area ($13.1 \pm 2.9\,mm^2$). The use of rhBMP-2 led to significant increases in new bone area for both VCMX (3.9 ± 1.1 vs. $1.6 \pm 1.3\,mm^2$, $p = 0.003$) and ACS (1.8 ± 0.8 vs. $1.0 \pm 0.6\,mm^2$, $p = 0.035$). Notably, the proportion of new bone in the total augmented region was comparable between the VCMX/rhBMP-2 and ACS/rhBMP-2 groups ($p > 0.05$).

Conclusion: rhBMP-2-loaded VCMX enhances bone regeneration in sinus augmentation, suggesting that its volume maintenance may contribute to the improved clinical and radiographic outcomes.

1 | Introduction

Bone regeneration can be enhanced by the combined use of grafting materials and biologic mediators. Among these, bone morphogenetic proteins (BMPs) have emerged as a viable strategy, as they stimulate mesenchymal progenitor cell migration and osteoblast differentiation (Galarraga-Vinueza et al. 2024). First described by Urist in 1965 (Urist 1965) and later molecularly identified by Wozney and colleagues (Wozney et al. 1988), BMPs were recognised for their unique osteoinductive potential. Based on the evidence from the clinical studies showing promising outcomes in alveolar ridge

Chae-Eun Kim and Seung-Hyun Park contributed equally to the writing of this manuscript.

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reconstruction and peri-implant augmentation (Sigurdsson et al. 1997; Wikesjö et al. 2005), recombinant human bone morphogenetic protein-2 (rhBMP-2) has since been applied in numerous clinical indications.

Until now, various types of carrier materials for rhBMP-2 have been investigated to enhance its effectiveness (Boyne et al. 2005; Cha et al. 2014; Lim et al. 2021). An ideal carrier should degrade in synchrony with new bone formation, neither persisting too long to impede bone remodelling, nor degrading too rapidly to compromise defect stability (Rao et al. 2013). Among the different carriers, an absorbable collagen sponge (ACS) has proven its strong osteoinductive potential and excellent biocompatibility, as well as favourable adsorption of growth-related cells and macromolecules (Geiger et al. 2003). ACS, currently the only FDA-approved delivery vehicle for rhBMP-2, has shown clinical success in maintaining alveolar ridge morphology and in sinus augmentation (Boyne et al. 2005; de Freitas et al. 2015; Fiorellini et al. 2005; Kuchler et al. 2017; Triplett et al. 2009). However, the limited volume stability of ACS has also been recognised as a drawback, prompting the development of strategies to enhance its mechanical support, such as combining ACS with non-resorbable scaffolds (Lee et al. 2017).

Increasing rhBMP-2 concentration on scaffolds has been attempted to enhance its performance. However, this poses risks of local and systemic complications, including swelling, bruising, ectopic bone, cystic changes and immune reactions (Boyne et al. 2005). To overcome these issues, recent strategies have focused on lowering the concentration of rhBMP-2. Several preclinical studies have demonstrated effective bone regeneration with doses as low as 0.01–0.05 mg/mL (Cha et al. 2021; Han et al. 2021; Kim et al. 2021), or on controlling the release kinetics to maintain localised activity (Han et al. 2021; Kim et al. 2024). Despite extensive studies using varying rhBMP-2 doses (ranging from 0.01 to 1.5 mg/mL), the optimal dose for craniofacial indications has not yet been established; also, the limited ability to effectively absorb and release rhBMP-2 remains an unresolved issue. Accordingly, developing a modular system enabling sustained release from defect-specific scaffolds remains crucial for improving the safety and efficacy of rhBMP-2-based bone regenerative therapies.

Among alternative carriers, volume-stable collagen matrix (VCMX) has gained attention for its enhanced structural integrity and controlled degradation (Thoma et al. 2010, 2016). A subsequent preclinical study in beagles demonstrated that VCMX placed in intrabony defects contributed to the regeneration of new bone, cementum and periodontal ligament, while also enhancing angiogenesis, indicating its intrinsic scaffold properties beneficial for both hard- and soft-tissue regeneration (Imber et al. 2021). Beyond its primary indication for soft-tissue augmentation, VCMX has also been reported to serve as an effective carrier for growth factors such as TGF-β1, PDGF-BB, rhPDGF-BB, FGF-2 and GDF-5 (Asparuhova et al. 2021). However, the use of VCMX in combination with growth factors for in vivo regenerative procedures, particularly peri-implant augmentation, has yet to be investigated. Further evaluation is needed to assess the potential of VCMX as an rhBMP-2 carrier for bone regeneration.

The aim of this study was to assess the feasibility of using VCMX as an rhBMP-2 delivery system. Specifically, the following were investigated: (1) the release kinetics of rhBMP-2 from VCMX and (2) its capacity to promote new bone formation and maintain graft volume in a rabbit sinus augmentation model, in comparison with ACS.

2 | Materials and Methods

2.1 | In Vitro Release Profile of rhBMP-2

To assess the release kinetics of rhBMP-2 from VCMX (Fibrogide, Geistlich, Wolhusen, Switzerland) and ACS (Teruplug, Terumo Biomaterials Co., Tokyo, Japan), a solution was prepared by diluting 0.1 g of rhBMP-2 (Cowell BMP, Cowell Medi Co., Busan, Republic of Korea) in 10 mL of 1× phosphate-buffered saline (PBS) to a final concentration of 0.01 g/mL. This concentration was chosen as suitable for in vitro release evaluation, while also being supported by a previous in vivo study identifying 0.01 g/mL as the minimum osteogenic dose in rabbit calvaria (Han et al. 2021). Each piece was placed in a 24-well plate and soaked with 200 μL of the rhBMP-2 solution for 5 min, a duration considered sufficient for rhBMP-2 loading based on the previous study (Lim et al. 2021), until complete adsorption was visually confirmed.

After absorption, the materials were transferred to Transwell inserts placed in 24-well plates containing 800 μL of 1× PBS and incubated at 37.5°C. At predetermined time points (10 min, 1 h, 3 h, 5 h, 8 h and Days 1–7), the entire release medium was collected and replaced with fresh PBS. The collected samples were stored at −80°C until analysis. The cumulative amount of rhBMP-2 released was quantified by enzyme-linked immunosorbent assay (ELISA). From Day 1 to Day 7, the PBS in each well was refreshed daily to continue monitoring the release.

2.2 | In Vivo Sinus Augmentation in a Rabbit Model

2.2.1 | Study Design

The study design and surgical methods were previously described in detail (Paik et al. 2022). Fifteen New Zealand white rabbits were included, each undergoing bilateral maxillary sinus augmentation. For each rabbit, the maxillary sinuses were randomly assigned using a web-based software (sealedenvelope.com) to one of the following groups: (i) VCMX soaked with 200 μL of saline (VCMX-alone group); (ii) VCMX loaded with 200 μL of rhBMP-2 (0.1 mg/mL) (VCMX/rhBMP-2 group); (iii) ACS soaked with 200 μL of saline (ACS-alone group); and (iv) ACS loaded with 200 μL of rhBMP-2 (0.1 mg/mL) (ACS/rhBMP-2 group). All graft materials were trimmed to a uniform size of 10 × 5 × 6 mm prior to loading. The surgical procedure was performed by one surgeon (J.-K.C.), who was necessarily aware of the allocated materials, while outcome analyses were performed by an independent investigator (C.-E.K.) in a blinded manner. All experimental protocols and procedures were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of Yonsei University Health System, Seoul,

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Republic of Korea (approval no. 2023-0191). Throughout the study, the care and use of animals were conducted in strict accordance with national and institutional regulations, including the Animal Protection Act and Laboratory Animal Act, as well as the ARRIVE guidelines.

2.2.2 | Surgical Procedure

General anaesthesia in rabbits was maintained with isoflurane inhalation following induction with alfaxalone, with further details provided in Appendix S1.

Incision was made along the midline on the nasal bone, followed by full-thickness elevation. Bilaterally circular windows of diameter 5.5 mm were prepared in each sinus with a trephine bur (C Reamer, Neobiotech, Seoul, Republic of Korea). The bone plates were removed from the sinus membrane and Schneiderian membranes were elevated with periosteal elevators. Each sinus received one of the experimental materials (VCMX or ACS, 10 × 5 × 6 mm). In the VCMX and ACS groups, either 200 μL of saline or rhBMP-2 solution (0.1 mg/mL) was applied accordingly (Figure 1). After graft application, the removed bone plate was repositioned, and the periosteum flap was primarily closed with suture using 6–0 absorbable monofilament suture material (Monosyn, B-Braun, Center Valley, PA, USA). Sutures were removed 7 days after surgery. All animals received antibiotics (enrofloxacin 5 mg/kg; Baytril, Elanco) once daily via subcutaneous injection for 1 week post surgery (7 days/sid, sc) (Paik et al. 2022). The animals were euthanised 4 weeks postoperatively.

2.2.3 | Sample Size Calculation

The required sample size for the experiment was estimated using the software G*Power v. 3.1.9.7 (Heinrich-Heine-Universität Düsseldorf, Germany). Based on the previous rabbit sinus model study assessing the regenerative efficacy of rhBMP-2, which showed a significantly higher new bone volume in the test group (107.28 ± 36.44 mm^3) compared to the control group (74.56 ± 15.20 mm^3) at 12 weeks in micro-computed radiographic analysis (Cha et al. 2021), an effect size of 1.19 was calculated. Considering the power of 80% and the alpha level of 0.05, a minimum number of 13 rabbits (two sites in each animal) was required. Based on an assumed dropout rate of 10%, a total of 15 rabbits (two sites in each rabbit, 30 sites in total) were deemed necessary for the experiment.

2.2.4 | Micro-Computed Tomographic Analysis

Following euthanasia, harvested specimens were fixed in 10% formalin and subjected to radiographic analysis. Each sample was positioned to centre the region of interest (ROI) and scanned using a high-resolution micro-computed tomography (micro-CT) system (SkyScan 1173; Bruker-CT, Kontich, Belgium). The scanning conditions were set as follows: tube voltage 130 kVp; tube current 60 μA; 1 mm aluminium filter; exposure time 500 ms; image resolution 2240 × 2240 pixels; pixel size 30.00 μm; and rotation step 0.2°. A total of 800 high-resolution images were acquired by rotating over 180°. The scanned dataset was reconstructed into three-dimensional (3D) images (2240 × 2240 pixels, Nrecon Ver 1.7.0.4, Bruker-CT) and alignment of axis with Dataviewer Ver. 1.5.1.2, Bruker-CT.

The ROI was defined as the augmented sinus cavity, bounded superiorly by the Schneiderian membrane and laterally and inferiorly by the native sinus walls, as described in previous studies (Cha et al. 2021; Yoon et al. 2017). The total augmented volume (TAV, mm^3) was determined by applying grey scale thresholds (0–255). Within this range, new bone volume (NBV, mm^3) was defined by thresholds of 35–255, and non-mineralized tissue volume (NMV, mm^3) by 0–34.

2.2.5 | Histomorphometric Analysis

After micro-CT scanning, the samples were decalcified with 5% formic acid for 14 days and embedded in paraffin after dehydration. The histological samples were sectioned at a thickness of 5 μm, and the central-most section that corresponded to the micro-CT slice was selected for analysis. The sectioned blocks were stained with Masson's trichrome. Histological slides were examined using CaseViewer software (3DHISTECH; Budapest, Hungary), and histomorphometric analysis was conducted using Adobe Photoshop 2024 (Adobe Systems; San Jose, CA, USA). One investigator (C.-E.K.) performed all analyses after several rounds of calibration using histological images from other studies, with intra-class correlation coefficient in the final round reaching over 0.9 ($p < 0.05$). Then, analyses using the present study materials

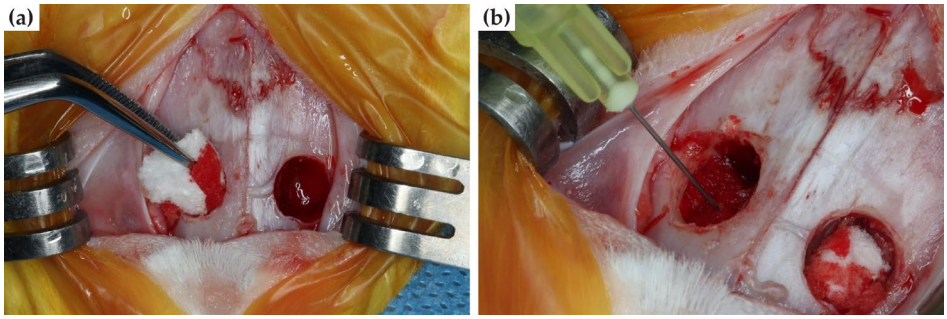

FIGURE 1 | Clinical photographs of surgical procedures. (a) Placement of allocated carrier material (10 × 5 × 6 mm) into each maxillary sinus. (b) Post-grafting application of 200 μL of saline or rhBMP-2 solution (0.1 mg/mL) onto the carrier material.

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were conducted with group assignments concealed from the examiner. The analyses were checked by another investigator (S.-H.P.) to ensure agreement.

Histomorphometric analysis was performed with the following parameters (Paik et al. 2020):

- Total augmentation area (TAA, mm^2): the area enclosed by the bone wall, Schneiderian membrane and the surgical access window.
- Newly formed bone area (NBA, mm^2) within the TAA: the newly formed bone was identified by its lamellar pattern.
- Residual graft material area (RMA, mm^2) within the TAA: the area where remnants of graft particles are observed.
- Non-mineralized tissue area (NMA, mm^2) within the TAA: the area within the TAA excluding the NBA and RMA.

2.2.6 | Statistical Analysis

Statistical analyses were conducted using SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA), and all data are presented as mean ± standard deviation (SD). For radiographic parameters (TAV, NBV, NMV) and histologic parameters (NBA, RMA, NMA), normality was not satisfied based on Kolmogorov–Smirnov and Shapiro–Wilk tests; therefore, the Kruskal–Wallis test was applied, followed by post hoc comparisons with Mann–Whitney tests. In contrast, TAA met the assumptions of normality (assessed by Kolmogorov–Smirnov and Shapiro–Wilk tests) and homogeneity of variance (assessed by Levene's test), allowing for one-way analysis of variance (ANOVA) with subsequent independent *t*-tests for pairwise comparisons.

3 | Results

3.1 | In Vitro Release Profile of rhBMP-2

Both the rhBMP-2-loaded VCMX and ACS groups exhibited a rapid release (Figure 2). The ACS group showed a slightly faster initial release compared to the VCMX group (ACS group: 10 min, VCMX group: 3 h), although the difference was not statistically significant. Following the peak release timepoint, rhBMP-2 levels gradually decreased in both groups over a 5-day period. The cumulative rhBMP-2 concentration (ng/mL) steadily increased in both groups, reaching a plateau by Day 5.

3.2 | In Vivo Sinus Augmentation in Rabbit

3.2.1 | Clinical Findings

All animals remained healthy throughout the study, with no complications observed. No adverse events, such as pus discharge, hematoma or swelling, were noted.

3.2.2 | Micro-CT Analysis

The augmented volume was greater in the VCMX group compared to the ACS group, with the VCMX group exhibiting a dome-shaped augmentation, while the ACS group showed a flatter shape (Figures 3 and 4). In both the VCMX/rhBMP-2 (Figure 4a) and ACS/rhBMP-2 (Figure 4b) groups, new bone formation was observed throughout the augmented space. In contrast, the VCMX alone (Figure 4c) and ACS-alone (Figure 4d) groups exhibited more non-mineralised areas within the augmented volume, indicating less bone formation.

Radiographic outcomes for each group are presented in Figure 5 and Tables S1 and S2. Overall, rhBMP-2 loading resulted in significantly higher values for TAV, NBV and NMV in both carriers ($p < 0.05$). In particular, the VCMX/rhBMP-2 group achieved the highest TAV and NBV values, showing significantly greater gains compared to ACS/rhBMP-2 ($p < 0.01$) (Table S2). Notably, NBV/TAV did not differ significantly with rhBMP-2 loading or between carriers ($p > 0.05$).

3.2.3 | Histological and Histomorphometric Analysis

Histological analysis showed the VCMX group to have a dome-like augmented area, whereas the ACS group displayed a flatter and, at times, finger-like augmented area (Figure 6). The

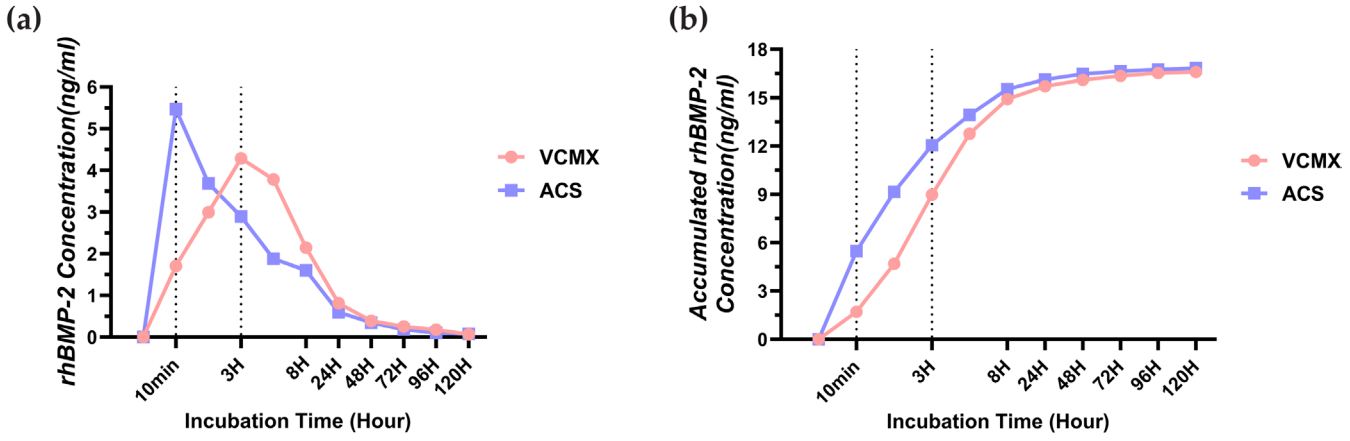

FIGURE 2 | In vitro release profile of rhBMP-2. (a) rhBMP-2 concentration (ng/mL) over time in the VCMX and ACS groups. (b) Cumulative rhBMP-2 concentration (ng/mL) in the VCMX and ACS groups.

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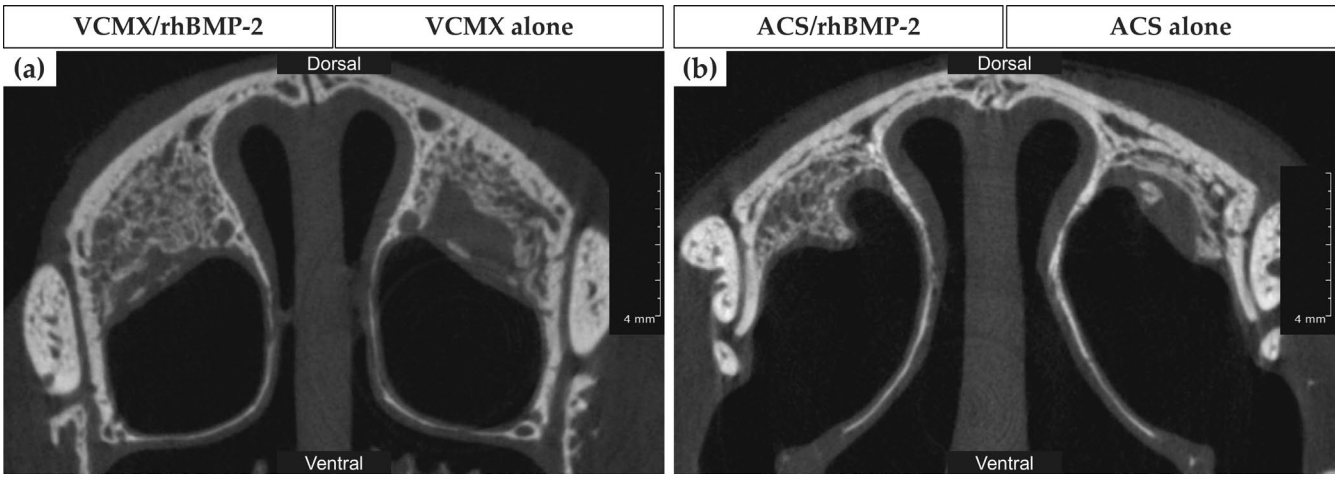

FIGURE 3 | Representative cross-sectional views of the augmented sinus. (a) VCMX/rhBMP-2 group (left) and VCMX-alone group (right). (b) ACS/rhBMP-2 group (left) and the ACS-alone group (right).

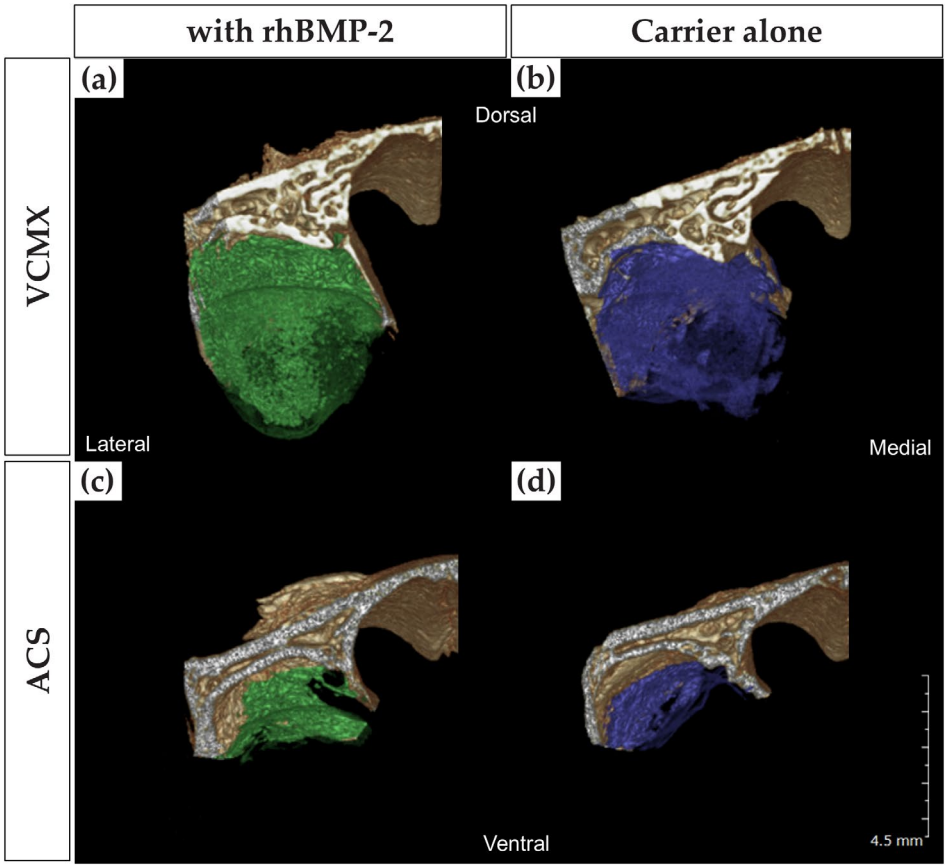

FIGURE 4 | Representative three-dimensional reconstructed micro-computed tomographic images of the augmented sinus. (a) VCMX/rhBMP-2 (green) group. (b) VCMX-alone (blue) group. (c) ACS/rhBMP-2 (green) group. (d) ACS-alone (blue) group.

VCMX/rhBMP-2 group showed greater new bone formation in the augmented area (Figure 6a), while the VCMX-alone group showed less new bone formation and a larger residual material area (Figure 6b). Additionally, the ACS/rhBMP-2 group showed new bone formation across the entire augmented area (Figure 6c) compared to the ACS-alone group (Figure 6d).

Histomorphometric analyses comparing VCMX and ACS revealed findings consistent with the radiographic outcomes (Table S3). ANOVA on TAA revealed a statistically significant difference between the groups ($12.5 \pm 3.1\,mm^2$ vs. $4.3 \pm 1.9\,mm^2$, $p < 0.0001$).

The results of the intergroup comparisons based on rhBMP-2 loading are presented in Figure 7 and Table S4. Briefly, NBA was significantly higher with rhBMP-2 loading in both carriers ($p < 0.05$), while RMA was significantly lower ($p < 0.05$), showing an opposite trend.

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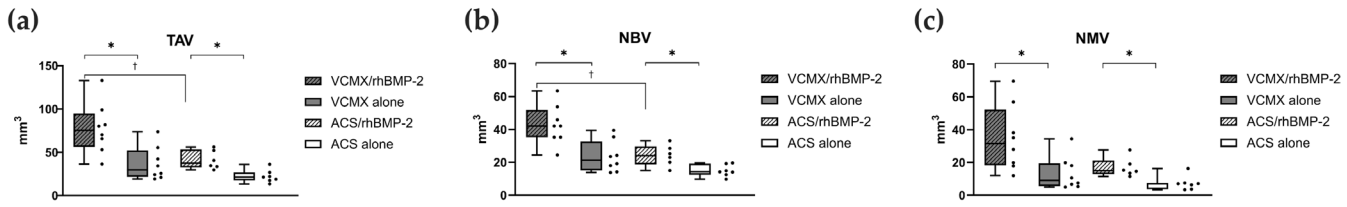

FIGURE 5 | Radiographic analysis of the augmented sinus volume. (a) TAV, total augmented volume; (b) NBV, new bone volume; (c) NMV, non-mineralised tissue volume. *Statistically significant difference between groups with and without rhBMP-2 application ($p < 0.05$). †Statistically significant difference between different carrier types ($p < 0.05$).

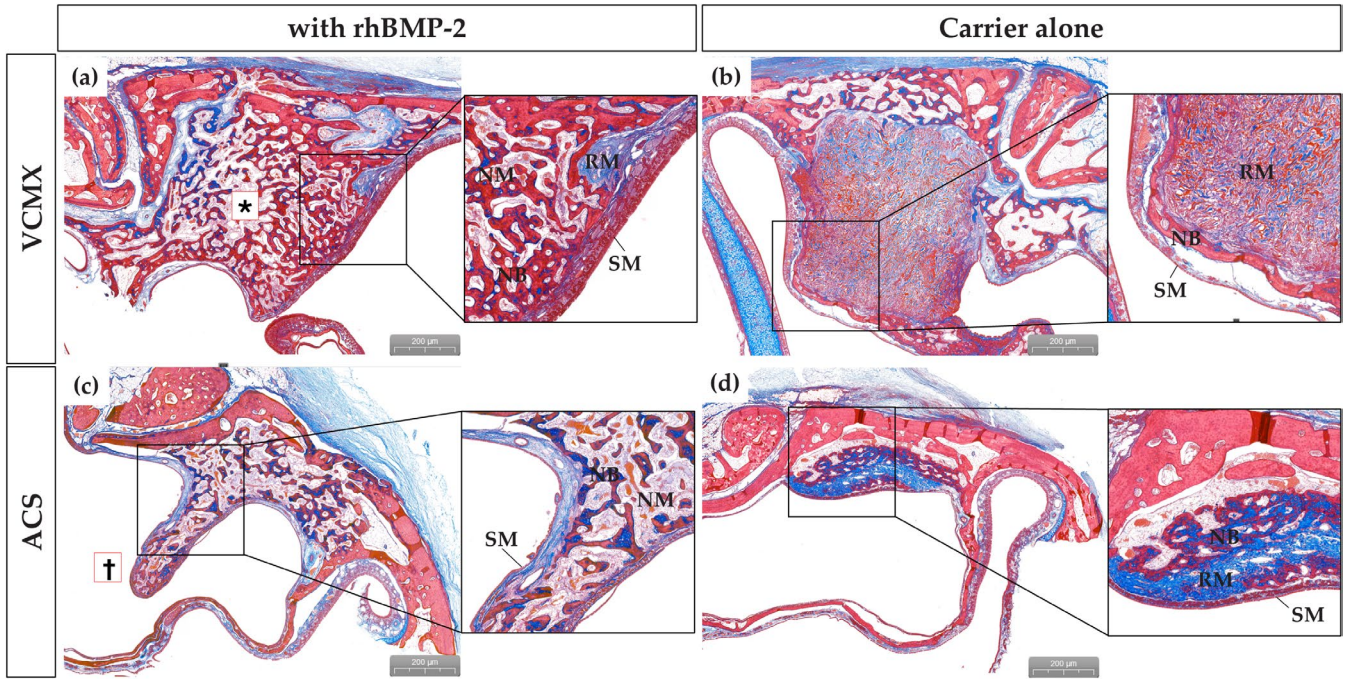

FIGURE 6 | Representative histological sections. (a) VCMX/rhBMP-2, (b) VCMX alone, (c) ACS/rhBMP-2 and (d) ACS alone. NB, newly formed bone; RM, residual graft material; NM, non-mineralised tissue; SM, sinus membrane. Dome-like shape of residual collagen matrix was observed in groups with VCMX (*), while finger-like projection was observed in groups with ACS (†).

It should also be noted that statistically significant differences were observed between the rhBMP-2-loaded groups across all variables (VCMX/rhBMP-2 vs. ACS/rhBMP-2; $p < 0.05$), with the VCMX/rhBMP-2 group showing higher values. Similar trends were observed between the VCMX-alone and ACS-alone groups, except for NBA, which did not differ significantly between the two groups ($p = 0.463$). Additionally, for NBA/TAA, a significant increase was observed only with VCMX when rhBMP-2 was loaded ($p = 0.004$), whereas ACS with rhBMP-2 did not differ from ACS-alone ($p = 0.103$). Between carriers, NBA/TAA was comparable in the rhBMP-2-loaded groups ($p = 0.260$) but higher with ACS than VCMX among the carrier-alone groups ($p = 0.015$).

4 | Discussion

This study was designed to test the hypothesis that VCMX, owing to its superior physical stability compared to an ACS, would lead to a significant increase in the total augmented area when applied for sinus augmentation. The current findings predominantly demonstrate that (1) VCMX exhibited a rhBMP-2 release pattern similar to that of ACS, but with a slightly delayed peak; (2) rhBMP-2 significantly enhanced bone formation in both VCMX and ACS groups; and (3) VCMX resulted in a larger augmented area and volume, as well as reduced postoperative shrinkage at 4 weeks compared to ACS. In summary, these results suggest that VCMX may serve as a promising carrier for rhBMP-2 for bone augmentation.

A recent in vitro study reported that VCMX shows advantageous properties in growth factor adsorption and release kinetics, indicating its potential as a carrier for rhBMP-2 (Asparuhova et al. 2021). The volume maintenance of this biomaterial, along with the active migration and proliferation of human oral fibroblasts and periodontal ligament cells into the collagen matrix, facilitates a robust bone regeneration process. The study demonstrated sustained release of growth factors (particularly PDGF-BB and FGF-2) up to 12 days after the regenerative procedure, with only partial release—39.2% for GDF-5 and 64.1% for FGF-2—within the 3–24-h period. In the present study, a delayed peak release was observed with VCMX (at 3 h) compared to ACS (at 10 min), yet the overall release patterns between the two did not differ significantly. These observations suggest that factors

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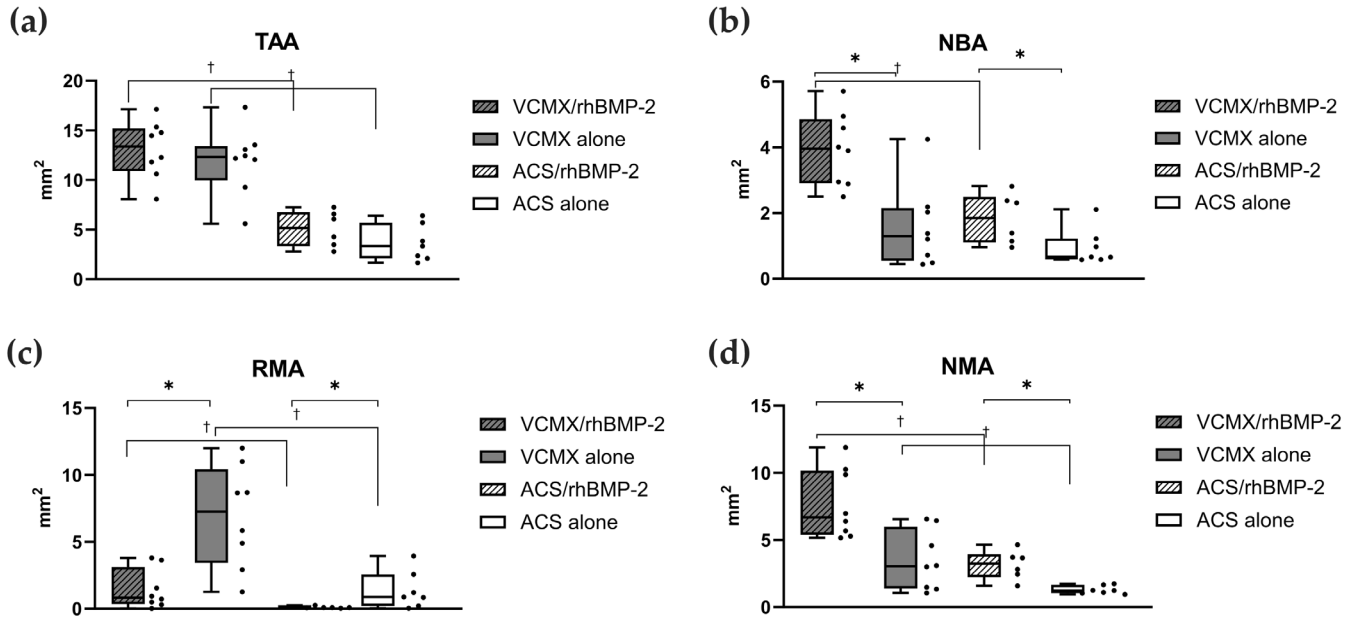

FIGURE 7 | (a) Histomorphometric analysis of the augmented sinus area. TAA, total augmented area; (b) NBA, new bone area; (c) RMA, residual graft materials area; (d) NMA, non-mineralized tissue area. *Statistically significant difference between groups with and without rhBMP-2 application ($p < 0.05$). †Statistically significant difference between different types of carriers ($p < 0.05$).

other than release kinetics, such as structural characteristics of the carriers, may influence subsequent bone regeneration.

Radiographic outcomes of sinus augmentation with rhBMP-2 have been reported to vary depending on the carriers used (Galarraga-Vinueza et al. 2024). In the previous review, ACS alone yielded lower volumetric stability than when combined with autogenous or allogeneic bone (de Freitas et al. 2015), suggesting the need for carriers that provide longer term volume maintenance. Lim et al. demonstrated a significant additive effect on TAV at 12 weeks when rhBMP-2 was added to a collagenated porcine bone block in a rabbit calvarial model (H.-C. Lim et al. 2023), which was consistent with previous findings showing significant TAV differences at 4 and 12 weeks based on BMP-2 application in a rabbit sinus model (Cha et al. 2021). In the present study, both VCMX and ACS groups showed a significant increase in TAV when BMP-2 was applied; notably, the VCMX/rhBMP-2 group exhibited significantly greater TAV and NBV than the ACS/rhBMP-2 group, likely attributable to the superior volume-maintaining properties of VCMX (Table S2).

Histological analyses in previous studies using BMP-2 have raised controversy over whether new bone formation occurs uniformly throughout the grafted area. Kang et al. reported the presence of central bone voids in sinus augmentation using hydroxyapatite/β-tricalcium phosphate (HA/BCP) (Kang et al. 2016), and a meta-analysis concluded that the clinical and histometric benefits of adjunctive rhBMP-2 use in sinus augmentation remain inconclusive (Lin et al. 2016). While core ossification was observed in a rabbit sinus model using collagenated porcine bone mineral (CPBM) (Cha et al. 2021), a subsequent in vivo study using collagenated BCP reported that mineralised bone formation was primarily localised near the periosteum (Kim et al. 2021). In the present study, the VCMX/rhBMP-2 group exhibited a larger NBA at 4 weeks compared with the VCMX-alone group, indicating a significant additive effect of rhBMP-2 (Table S4). This outcome is consistent with previous findings in a rabbit sinus model using CPBM (Cha et al. 2021). While the proportion of new bone formation (NBA/TAA) was significantly lower in the VCMX-alone group compared to the ACS-alone group, this difference was mitigated after the loading of rhBMP-2 because of a substantial increase in both groups (Table S4). Notably, whereas new bone formation in the ACS group was confined to peripheral areas adjacent to the Schneiderian membrane or native bone (Figure 6c,d), the VCMX/rhBMP-2 group exhibited more extensive new bone formation throughout the grafted material (Figure 6a), a finding not observed in previous studies. These observations suggest that the initial rhBMP-2-driven osteoinductive process may have contributed to substantial bone regeneration within the VCMX scaffold, indicating that VCMX could serve as an effective collagen matrix carrier for rhBMP-2.

This study had several limitations that should be acknowledged. First, this study focused on early-stage bone formation at 4 weeks, which may not fully represent long-term bone remodelling and implant stability. Previous studies have shown that the initial phase of bone formation, dominated by woven bone, transitions to lamellar bone during remodelling, which is crucial for achieving optimal mechanical stability and long-term success of implants (Araújo and Lindhe 2005). While early results are promising, the long-term performance of the newly formed bone, especially its capacity to support functional loading and implant stability, remains uncertain. Second, caution is needed when interpreting the release kinetics of rhBMP-2. In vitro release profiles may differ substantially from in vivo conditions where intraoperative bleeding and local enzymatic activity, such as collagenase, can influence the release dynamics. Third, although VCMX demonstrated superior volume maintenance compared with ACS at 4 weeks, previous reports have indicated that it may undergo gradual shrinkage during healing (Thoma et al. 2023). In the present study, VCMX loaded

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with rhBMP-2 showed markedly reduced volumetric shrinkage, along with a significant increase in the proportion of new bone area (Table S4), suggesting an alteration of the shrinkage pattern after rhBMP-2 loading. Such alteration may enhance the long-term stability of sinus augmentation. Further studies are required to determine whether these early outcomes translate into durable and clinically relevant benefits (Donos et al. 2023).

5 | Conclusion

rhBMP-2-loaded VCMX enhances bone regeneration in a sinus augmentation model demonstrating superiority compared to the traditional ACS carrier for rhBMP-2. This appears to be primarily attributed to its favourable volume maintenance rather than its release kinetics.

Author Contributions

Chae-Eun Kim: data curation, formal analysis, writing – original draft. **Seung-Hyun Park:** investigation, writing – original draft. **Kyeong-Won Paeng:** formal analysis, data curation, investigation. **Lorenzo Tavelli:** validation, writing – review and editing. **David T. Wu, Daniel S. Thoma** and **Ronald E. Jung:** validation, writing – review and editing. **Ui-Won Jung:** conceptualisation, methodology, supervision, writing – review and editing. **Jae-Kook Cha:** conceptualisation, methodology, validation, investigation, supervision, funding acquisition, project administration, visualisation, resources.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

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