Suppl 1. Efficacy and Advancements in Dentistry With HA and BoNT-A

| # | Study | Year | Clinical indications | Dosage/treatment | Efficacy measures | Improvement in dentistry | Patient satisfaction | Results | Safety measures | Key findings | Study limitations | Clinical implications |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1 | Alcantara et al [13] | 2018 | Bilateral extraction of mandibular premolars | 1% HA (1 mL) | Bone formation, fractal dimension values | Yes | NR | Treated sockets showed higher bone formation (58.17% vs. 48.97%) and fractal dimension (1.098 vs. 1.074) compared to controls at 30 days post-op. | NR | No significant difference in alveolar dimensions (P > 0.05). 1% HA gel accelerates bone repair in human dental sockets. | - Unequal distribution of gingival index (GI) levels at baseline.- Lack of a positive control group (e.g., chlorhexidine users).- Short study duration (21 days).- Need for future studies with radiographic and histological evaluations. | - HA gel may aid in accelerating bone repair post-tooth extraction.- Further research should explore HA use in varied dental conditions and in combination with other materials. |
| 2 | Boccalari et al [14] | 2022 | Plaque-induced gingivitis | Mouth rinse with H2O2 (1.80%) and HA (0.10%) | Plaque index, gingival index | NR | Increased taste and odor satisfaction | Combination rinse more effective against gingivitis, with better taste and odor scores. | No side effects registered. | Novel mouth rinse with HA and H2O2 reduces gingival inflammation without affecting plaque control. | - Unequal GI levels at baseline.- Lack of a positive control group (e.g., chlorhexidine users).- Short study duration (21 days). | - Mouth rinse with HA and H2O2 can assist in maintaining healthy gums and resolving gingivitis.- Further randomized controlled trials are warranted to compare its efficacy with chlorhexidine. |
| 3 | Castano-Joaqui et al [15] | 2021 | TMJ internal derangement | High molecular weight HA (20 mg/mL) | VAS joint pain score, MMO, OHRQoL | Yes | Yes | Significant MMO increase, reduced pain, improved OHRQoL up to 12 months post-op. | NR | No benefit observed from hyaluronic acid as adjuvant therapy to arthroscopy at 3 - 12 months follow-up. | - Limited participants precluded subgroup analysis.- Psychological and dental factors not measured. | - Hyaluronic acid injection during TMJ arthroscopy shows no benefit beyond 3 months.- Further studies are needed to refine its indications in TMJ disorders. |
| 4 | Costa et al [16] | 2022 | Gum recession or exposed gums | BTX-A injections (2 U per point) | Reduction in exposed gingiva, EMG, satisfaction | Yes | Yes | Significant reduction in exposed gingiva, muscle activity, and increased satisfaction up to 25 weeks post-treatment. | No adverse effects reported. | Increasing BTX-A injection points prolongs effect on gingival display reduction without intensity increase. | - High patient dropout rate compromised data integrity. | - Increasing BTX-A injection points may extend treatment effectiveness.- Different injection protocols should be explored in future studies. |
| 5 | De la Torre Canales et al [17] | 2020 | Temporomandibular disorder | BoNT-A injections (100 U) | VAS pain, PPT, EMG, masticatory performance | Yes | NR | Significant pain reduction, increased PPT, decreased muscle activity with BoNT-A compared to controls. | Dose-related adverse effects of BoNT-A. | BoNT-A is as effective as OA for persistent MFP, but dose-related adverse effects favor conservative treatments initially. | - Longer follow-up periods needed to assess BoNT-L efficacy over time.- Limited sample selection restricts generalizability. | - Oral appliances remain first-line therapy for persistent MFP due to lower adverse effect risk.- BoNT-A may be considered in patients unresponsive to conservative treatments, with caution due to dose-related adverse effects. |
| 6 | De la Torre Canales et al [18] | 2022 | Myofascial pain | BoNT-A injections (low, medium, high doses) | Mandibular motion, muscle pain | Yes | NR | BoNT-A groups showed improved mouth opening, reduced muscle pain compared to controls at 180 days. | NR | BoNT-A improves mandibular range of motion and reduces muscle pain in persistent MFP, but caution is advised due to study limitations. | - Restricted study population without gender comparison.- Larger studies needed with lower BoNT-A doses and comparison with other treatments. | - BoNT-A may improve symptoms in persistent MFP, but further research with larger samples and lower doses is recommended. |
| 7 | De la Torre Canales et al [19] | 2022 | Myofascial pain | BoNT-A injections (different doses) | Self-perceived pain, pain sensitivity, muscle thickness | Yes | NR | Significant pain reduction, increased pain threshold, reduced muscle thickness up to 6 years post-treatment. | NR | Single injection of BoNT-A reduces pain long-term in persistent MFP patients. | - Convenience sample without gender comparison.- Larger sample size required for future studies. | - BoNT-A injection may provide long-term pain relief in persistent MFP, possibly through central pain mechanisms.- Larger studies are needed to confirm these findings. |
| 8 | Kokash et al [20] | 2023 | Trismus and swelling after tooth extraction | Collagen with/without HA | Rate of trismus, swelling scores | NR | NR | Hyaluronic acid reduced trismus and swelling compared to collagen alone. | NR | Adding hyaluronic acid to collagen reduces facial swelling and trismus post-impacted lower third molar extraction. | - Lack of laboratory or histological examinations. | - Hyaluronic acid with collagen can help reduce post-extraction swelling and trismus, benefiting surgical outcomes. |
| 9 | Mamajiwala et al [21] | 2021 | Chronic periodontitis | HA gel + OFD | PI, GI, PD, CAL, GR | Yes | NR | Test group showed greater CAL gain, bone defect fill, and PD reduction compared to controls at 12 months. | NR | HA gel with open flap debridement improves clinical and radiographic outcomes over 12 months. | - Inclusion of only contained defects limits assessment of true regenerative potential.- Variations in defect morphology may introduce bias.- Adjacent furcation defects may influence results.- Gel washout after delivery not controlled.- Optimal gel dose and concentration unknown. | - HA gel adjunct to debridement may enhance periodontal outcomes. |
| 10 | Park et al [22] | 2022 | Masseter muscle hypertrophy | BoNT injections alone/with oral appliance | Reduction in masseter bulkiness height | NR | NR | Reduction in bulkiest height in both groups, more significant with oral appliance at 24 weeks. | NR | OA normalizes masseter muscle activity after BoNT injection for lower face contouring. | - Small sample size limits generalizability.- Longer follow-up needed for comprehensive assessment.- Lack of control for bruxism may affect results. | - BoNT combined with OA may be effective for lower face contouring.- Longer-term effects and comparison with other appliances should be studied. |
| 11 | Shemais et al [23] | 2021 | Excessive gingival display | Zinc supplement with/without BTX-A | Reduction in gingival display, patient satisfaction | Yes | Yes | Significant reduction in gingival display with zinc supplement + BoNT-A, high satisfaction. | NR | Zinc supplementation prolongs BTX-A effect on gingival display, maintaining decreased display long-term. | - High dropout rate compromises data integrity. | - Oral zinc supplements may extend BTX-A efficacy in correcting gummy smile. |
| 12 | Steenen et al [24] | 2023 | Lip augmentation | Various HA dermal fillers | Lip height, appearance appraisal, social function, psychological well-being | Yes | Yes | All fillers increased lip height and appearance appraisal, with differences in effectiveness and social function improvement. | Juvederm associated with higher side effects than Stylage. | Statistically significant but potentially clinically irrelevant differences between fillers observed. | - Not all statistically significant differences may be clinically relevant. | - Duration, patient satisfaction, and quality of life improvements seen with both fillers.- Future trials should consider additional outcome measures. |

BTX-A/BoNT-A: botulinum toxin type A; HA: hyaluronic acid; NR: not reported; TMJ: temporomandibular joint; MMO: maximum mouth opening; OHRQoL: oral health-related quality of life; VAS: visual analog scale; PPT: pressure pain threshold; EMG: electromyography; OFD: open flap debridement; OA: oral appliance; PI: plaque index; GI: gingival index; PD: probing depth; CAL: clinical attachment level; GR: gingival recession.