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CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Hyaluronic Acid Injection for Facial Grooves or Wrinkles: Clinical Effectiveness, Safety, and Guidelines

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Research Questions

1. What is the clinical effectiveness of injected hyaluronic acid for facial grooves or wrinkles?
2. What is the safety of injected hyaluronic acid for facial grooves or wrinkles?
3. What are the evidence-based guidelines regarding injected hyaluronic acid for facial grooves or wrinkles?

Key Findings

One systematic review and 20 randomized controlled trials were identified regarding the the clinical effectiveness and safety of injected hyaluronic acid for facial grooves or wrinkles. No relevant evidence-based guidelines were identified.

Methods

A limited literature search was conducted on key resources including Medline via OVID, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and March 1, 2019. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with facial grooves or wrinkles
Intervention	Hyaluronic acid
Comparator	Q1,2: Other dermal fillers Q3: No treatment
Outcomes	Q1: Clinical effectiveness (e.g., visual improvement of area) Q2: Safety (e.g., adverse events, necrosis, migration of filler) Q3: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

One systematic review and 20 randomized controlled trials were identified regarding the the clinical effectiveness and safety of injected hyaluronic acid for facial grooves or wrinkles. No relevant health technology assessments, meta-analyses, or evidence-based guidelines were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

One systematic review[1] and 20 randomized controlled trials[2-21] were identified regarding the the clinical effectiveness and safety of injected hyaluronic acid for facial grooves or wrinkles. Detailed study characteristics are provided in Table 2.

Many of the randomized controlled trials found little or no difference between the intervention and comparator based on the wrinkle severity rating scale (WSRS) at their respective follow-up timeframe.[2,5-7,9,11,14,19-21] Similarly, for safety outcomes, most studies reported little or no differences between products.[5,6,8,9,11,12,14,15,17-21]

The reader may find it noteworthy that many of the randomized controlled trials are of a "split-face" design where all participants are receiving the intervention.[4-21]

No relevant evidence-based guidelines were identified.

Table 2: Summary of Included Studies

Author, Year	Study Characteristics; Intervention; Comparator	Outcomes	Results	Author Conclusions
Systematic Review				
Pascali, 2018[1]	N = 17 studies; Various dermal fillers and grafts; Varrious dermal fillers and grafts.	Efficacy for lip and perioral rejuvenation	NR in abstract	NR in abstract
Randomized Controlled Trials				
Hu, 2017[2]	N = 62 participants; HA; Autologous fat.	WSRS and GAIS assessed by evaluator and patient-self at various timepoints;	Evaluator scores for WSRS were no different until 12-month follow-up. Patient scores were similar;	"Both HA gel and autologous fat provide augmentation of NLFs. The magnitude and duration of NLF

Author, Year	Study Characteristics; Intervention; Comparator	Outcomes	Results	Author Conclusions
		AEs were recorded	Differences in AEs were obvious in early stages. Later stage ARs were similar.	correction appear to be similarly effective and safe within a period."[2]
Zhou, 2016[3]	N = 49 participants; Monophasic monodensified HA; Biphasic nonanimal stabilized HA.	Effectiveness; Safety.	Satisfactory outcome in NLF correction in both groups; A lesser amount of monophasic monodensified HA was necessary to achieve similar results as a the comparator; Effectiveness was maintained at 24-week follow-up in both groups.	"Both [monophasic monodensified HA] and [biphasic nonanimal stabilized HA] are effective for correcting NLF in Asian patients, producing satisfactory results. Monophasic monodensified [HA] provides similar satisfaction to [biphasic nonanimal stabilized HA] while requiring less injection volume."[3]
Dai, 2019[4]	N = 115 participants; Princess VOLUME; Restylane.	Safety; Effectiveness (WSRS, GAIS assessed by independent review committee and subjects)	The independent review committee assessed that the WSRS improvement rate reached 68.70% for Princess VOLUME and 52.17% for Restylane.	"This study confirms that [Princess VOLUME] is a safe and effective treatment for the correction of moderate-to-severe NLFs in Chinese subjects."[4]
Fino, 2019[5]	N = 59 participants; Ial System Duo; Belotero Basic/Balance.	WSRS; GAIS; Skin thickness.	No significant differences on skin thickness, subject's satisfaction, and AEs.	"The Ial System Duo achieves long-term permanence (more than 9 months confirmed by ultrasound) in correction of moderate and severe wrinkles, similar to Belotero Basic/Balance. Both products showed a high safety profile and a high degree of subject and physician satisfaction."[5]
Gold, 2018[6]	N = NR Novel HA gel;	WSRS.	The novel HA gel was non-inferior to the comparator;	"The Test Product is safe and non-inferior to the Comparator for the correction of

Author, Year	Study Characteristics; Intervention; Comparator	Outcomes	Results	Author Conclusions
	Non-animal stabilized HA gel;		No subject discontinued the study due to AEs.	nasolabial folds. The Test Product was associated with less swelling, pain, and overall severity of treatment-emergent adverse events than the Comparator."[6]
Hong, 2018[7]	N = 91 participants; IDHF-001; Restylane SubQ.	WSRS.	No significant difference in WSRS at 24 weeks.	"The novel HA filler IDHF-001 shows suitable characteristics and tolerability, widening the selection possibilities for clinicians and patients in the treatment of NLFs."[7]
Ascher, 2017[8]	N = NR HA_{ED}; HA_{PER}.	WSRS; Participant preference; Safety.	WSRS scores favoured HA_{ED} at three to 12 months; Participants preferred HA_{ED} at 12 months; Both products had few treatment-related AEs.	"To conclude, HA_{ED} was at least as effective and well tolerated for the treatment of severe NLFs as HA_{PER}."[8]
Kwon, 2017[9]	N = 72 participants; Monophasic HA; Biphasic HA.	Efficacy (WSRS); Safety (abnormal reactions).	Mean WSRS were 2.26 ±0.56 and 2.24±0.54 for the monophasic HA and biphasic HA respectively, at week 26; Both treatments were well tolerated.	"Despite a number of different rheological properties, monophasic HA is noninferior to biphasic HA in the treatment of moderate to severe NLFs for 52 weeks. Therefore, monophasic HA provides an alternative option for NLFs correction."[9]
Li, 2017[10]	N = 124 participants; Juvederm Ultra Plus (24mg/mL); Restylane (20mg/mL).	Allergan NLF Severity Scale; Investigator assessed response rate; Participant assessed response rate and preference.	Mean Improvements in NLF Severity Scale were 1.5 and 1.6 for Juvederm and Restylane respectively, at six months; Participant and investigator-assessed response rate were	"In this study in Chinese subjects, Juvederm Ultra Plus was safe and effective for correcting severe NLFs."[10]

Author, Year	Study Characteristics; Intervention; Comparator	Outcomes	Results	Author Conclusions
			similar; Participant preference favoured Juvederm.	
Rzany, 2017[11]	N = NR; HAEC; HARES.	Effectiveness (WSRS, participant preference); Safety (AEs).	Mean WSRS score change was similar; No difference in participant preference; Both were well tolerated.	"HAEC and HARES were effective and well tolerated for treatment of moderate NLFs."[11]
Trevidic, 2017[12]	N = NR; Art Filler Universal, Art Filler Fine Lines; Juvederm Ultra 3, First Lines Pure Sense.	Lemperle scale; Tolerability; GAIS; Wrinkle volumes, skin thickness and density.	NLF and crow's feet showed improvement at 30, 90, and 180 days. Treatments were well tolerated. GAIS improvements maintained until day 180.	"[Art Filler Universal] and [Art Filler Fine Lines] are noninferior to comparators. The methodology used represents a novel approach to augment existing clinical assessment of HA fillers."[12]
Kim, 2016[13]	N = 13 participants; Novel mannitol containing HA filler; Biphasic HA filler.	Genzyme grading scale; GAIS.	Genzyme grading scale scores were greater for the intervention at 12 and 24 weeks; At 12 weeks, GAIS scores were higher in the intervention group.	"The [mannitol containing HA filler] provides better efficacy and similar local tolerability compared with [biphasic HA filler] in 6 months following treatment for moderate and severe NLF."[13]
Noh, 2016[14]	N = 81 participants; PP-501-B; Restylane Perlane.	WSRS; GAIS.	No significant difference in WSRS scores. Both fillers were well tolerated.	"The new HA filler PP-501-B is safe and effective in the long term for the correction of moderate-to-severe NLFs, even after a second treatment."[14]
Wu, 2016[15]	N = 88 participants; BioHyalux; Restylane.	WSRS; Response rates; GAIS	At 13-15 months, response rates were similar and 60% of participants reported improvements with BioHyalux compared to 64% with Restylane. AEs were transient and	"BioHyalux had reliable safety and tolerance, and could be an effective injectable filler for correcting NLF."[15]

Author, Year	Study Characteristics; Intervention; Comparator	Outcomes	Results	Author Conclusions
			mild or moderate.	
Wu, 2016[16]	N = 104 participants; Juvederm Ultra (24mg/mL); Restylane (20mg/mL).	Allergan NLF Severity Scale; Investigator assessed response rate; Participant assessed response rate and preference.	Investigator-assessed response rates were similar and mean Improvements in NLF Severity Scale were 1.0 for both products, at six months; Participant-assessed response rate were and mean Improvements in NLF Severity Scale favoured Juvederm Ultra, at six months; Participant preference favoured Juvederm Ultra; Juvederm Ultra had fewer severe responses than Restylane.	"Juvederm Ultra is noninferior to Restylane and is a safe and effective treatment for correcting moderate NLFs in Chinese subjects."[16]
Galadari, 2015[17]	N = 40 participants; Novel biostimulatory polycaprolactone filler; Nonanimal stabilized HA filler.	WSRS; GAIS.	Greater improvements in WSRS and GAIS were achieved with the interventional filler compared to the nonanimal stabilized HA filler; Both products were equally safe and well tolerated.	"Our results suggest that [polycaprolactone]-based dermal fillers offer longer-lasting performance over [nonanimal stabilized HA]-based dermal fillers in NLFs treatment."[17]
Hyun, 2015[18]	N = NR; Poly-L-lactic acid filler; Biphasic HA filler.	WSRS; Safety.	WSRS mean improvement was 2.09 and 1.54 for the poly-L-lactic acid filler and biphasic HA filler, respectively, at week 24; Both products were well tolerated.	"[Poly-L-lactic acid filler] provides noninferior efficacy compared with HA 6 months after being used to treat moderate to severe nasolabial folds."[18]
Pak, 2015[19]	N = 67 participants; Neuramis Deep; Restylane.	WSRS; GAIS; Safety (AEs).	No significant difference in efficacy or safety.	"In conclusion, our results indicate that Neuramis Deep may be a safe, effective material for improving the nasolabial folds.

Author, Year	Study Characteristics; Intervention; Comparator	Outcomes	Results	Author Conclusions
				However, further studies are warranted to compare the tolerability of Neuramis Deep and Restylane based on histopathologic findings."[19]
Park, 2015[20]	N = 103 participants; PP-501-B; Restylane Perlane.	WSRS.	WSRS mean improvement was 1.87 and 1.92 for the PP-501-B and Restylane Perlane, respectively, at week 24; Both products were well tolerated.	"The new HA filler, PP-501-B, to the market, with suitable characteristics and ample safety profiles, will widen the selection of agents for physicians and patients because the purpose, area, and depth of filler injections vary."[20]
Rhee, 2014[21]	N =; Monophasic HA; Biphasic HA.	WSRS; Local safety.	WSRS mean improvement was 2.18 and 2.16 for the monophasic HA and biphasic HA, respectively, at week 24; Both products were well tolerated.	"Mono-HA has a non-inferior efficacy to bi-HA in the treatment of moderate to severe nasolabial folds."[21]

AE = adverse event; GAIS = global aesthetic improvement scale; HA = hyaluronic acid; NLF = nasolabial folds; NR = not reported; WSRS = wrinkle severity rating scale.

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

Alternative Facial Site Application

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Randomized Controlled Trials

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Split-Face Methodology

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Guidelines and Recommendations

No literature identified.

Appendix — Further Information

Systematic Reviews and Meta-analyses

Alternative Population –Application Other Than Wrinkles

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Alternative Intervention – Combination of Agents

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Randomized Controlled Trials

Alternative Intervention – Combination of Agents

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Non-Randomized Studies

Alternative Facial Site Application

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Alternative Population – Application Other Than Wrinkles

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Alternative Intervention – Combination of Agents

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