

# Safety of Intra-articular Hyaluronic Acid for Knee Osteoarthritis: Systematic Review and Meta-analysis of Randomized Trials Involving Over 8,000 Patients

## Supplement

**Supplement Table 1. Medline Search Strategy.**

<b>Study Design Search Terms</b>
1. Clinical Trial, pt
2. Clinical Trial, Phase I, pt
3. Clinical Trial, Phase II, pt
4. Clinical Trial, Phase III, pt
5. Clinical Trial, Phase IV, pt
6. Controlled Clinical Trial, pt
7. Multicenter Study, pt
8. Randomized Controlled Trial, pt
9. random*, ti, ab
10. placebo*, ti, ab
11. sham*, ti, ab
12. control*, ti, ab
13. saline*, ab
<b>Diagnosis Search Terms</b>
14. osteoarthriti*, ti, ab
15. osteoarthro*, ti, ab
16. gonarthriti*, ti, ab
17. gonarthro*, ti, ab
18. arthriti*, ti, ab
19. arthro*, ti, ab
20. osteoarthritis, majr
<b>Diagnosis Location Search Term</b>
21. knee*, mp
<b>Viscosupplementation Search Terms</b>
22. adant*, mp
23. arthrum*, mp
24. artz*, mp
25. biohy*, mp
26. durolane*, mp
27. euflexxa*, mp
28. gel-one*, mp
29. go-on*, mp
30. healon*, mp
31.hya-ject*, mp
32. hyalectin*, mp
33. hyalgan*, mp
34. hyaluron*, mp
35. hylan*, mp

36. hylastan*, mp
37. hymovis*, mp
38. kartilage*, mp
39. monovisc*, mp
40. nrd101*, mp
41. nuflexxa*, mp
42. orthovisc*, mp
43. ostenil*. mp
44. supartz*. mp
45. suplasyn*, mp
46. synvisc*, mp
47. viscosupplement*, mp
<b>Combination Terms</b>
48. or/1-13
49. or/14-20
50. or/21
51. or/22-47
52. and/48-51

**Supplement Table 2. Excluded Randomized Controlled Trials of Hyaluronic Acid Injection for Knee Osteoarthritis.**

<b>Study</b>	<b>Primary reason for exclusion</b>
Adams, 1995 <sup>1</sup>	No intra-articular injection in control group
Ahmad, 2018 <sup>2</sup>	Active control group (platelet-rich plasma injection)
Ardic, 2001 <sup>3</sup>	Sample size less than 30 in any group
Askari, 2016 <sup>4</sup>	Active control group (corticosteroid injection)
Atamaz, 2006 <sup>5</sup>	Sample size less than 30 in any group
Atay, 2008 <sup>6</sup>	Patients underwent knee surgery
Auerbach, 2002 <sup>7</sup>	Active control group (gaseous oxygen injection)
Bao, 2018 <sup>8</sup>	Sample size less than 30 in any group
Bayramoğlu, 2003 <sup>9</sup>	Sample size less than 30 in any group
Bellamy, 2005a <sup>10</sup>	Redundant with Reynauld (2002)
Bellamy, 2005b <sup>11</sup>	Redundant with Reynauld (2002)
Berenbaum, 2012 <sup>12</sup>	Active control group (HA injection)
Bisicchia, 2016 <sup>13</sup>	Active control group (corticosteroid injection)
Blanco, 2008 <sup>14</sup>	Sample size less than 30 in any group
Bragantini, 1987 <sup>15</sup>	Sample size less than 30 in any group
Buendia-Lopez, 2018 <sup>16</sup>	Active control group (platelet-rich plasma injection)
Bunyaratavej, 2001 <sup>17</sup>	Sample size less than 30 in any group
Butun, 2002 <sup>18</sup>	Sample size less than 30 in any group
Caborn, 2004 <sup>19</sup>	Active control group (corticosteroid injection)
Campos, 2017 <sup>20</sup>	Active control group (corticosteroid injection)
Caracuel, 2001 <sup>21</sup>	Sample size less than 30 in any group
Carrabba, 1995 <sup>22</sup>	Sample size less than 30 in any group
Chou, 2009 <sup>23</sup>	Active control group (HA injection)
Cogalgil, 2002 <sup>24</sup>	Sample size less than 30 in any group
Cohen, 1994 <sup>25</sup>	Sample size less than 30 in any group
Cole, 2017 <sup>26</sup>	Active control group (platelet-rich plasma injection)
Conrozier, 2009 <sup>27</sup>	Sample size less than 30 in any group
Conrozier, 2016 <sup>28</sup>	Active control group (HA injection)
Corrado, 1995 <sup>29</sup>	Sample size less than 30 in any group
Creamer, 1994 <sup>30</sup>	Sample size less than 30 in any group
Çubukçu, 2005 <sup>31</sup>	Sample size less than 30 in any group
Dahlberg, 1994 <sup>32</sup>	Sample size less than 30 in any group
Dallari, 2018 <sup>33</sup>	Active control group (polynucleotide injection)
DeCaria, 2012 <sup>34</sup>	Sample size less than 30 in any group
Di Martino, 2016 <sup>35</sup>	Patients underwent knee surgery
Dickson, 2001 <sup>36</sup>	Active control group (corticosteroid injection)
Diracoglu, 2009 <sup>37</sup>	Sample size less than 30 in any group
Ertürk, 2016 <sup>38</sup>	Active control group (HA injection)
Estades-Rubio, 2017 <sup>39</sup>	Active control group (HA injection)
Filardo, 2016 <sup>40</sup>	Patients underwent knee surgery
Forster, 2003 <sup>41</sup>	Patients underwent knee surgery
Frizziero, 2002 <sup>42</sup>	Active control group (corticosteroid injection)
Ghirardini, 1990 <sup>43</sup>	Sample size less than 30 in any group
Gigis, 2016 <sup>44</sup>	Active control group (HA injection)
Giarratana, 2014 <sup>45</sup>	Active control group (polynucleotide injection)

Graf, 1993 <sup>46</sup>	Active control group (mucopolysaccharide polysulphate injection)
Grecomoro, 1987 <sup>47</sup>	Sample size less than 30 in any group
Groppa, 2001 <sup>48</sup>	Sample size less than 30 in any group
Guler, 1996 <sup>49</sup>	Sample size less than 30 in any group
Guo, 2018 <sup>50</sup>	Active control group (HA injection)
Heybeli, 2008 <sup>51</sup>	Patients underwent knee surgery
Hizmetli, 2002 <sup>52</sup>	Sample size less than 30 in any group
Houseman, 2014 <sup>53</sup>	Active control group (corticosteroid injection)
Huang, 2005 <sup>54</sup>	No intra-articular injection in control group
Ishijima, 2014 <sup>55</sup>	No intra-articular injection in control group
Jones, 1995 <sup>56</sup>	Active control group (corticosteroid injection)
Jubb, 2003 <sup>57</sup>	Patients underwent multiple treatment cycles
Jüni, 2007 <sup>58</sup>	Active control group (HA injection)
Kahan, 2003 <sup>59</sup>	No intra-articular injection in control group
Kalay, 1997 <sup>60</sup>	Sample size less than 30 in any group
Kalman, 2008 <sup>61</sup>	Oral supplementation
Kaplunov, 2015 <sup>62</sup>	No relevant outcomes reported
Karatosun, 2005 <sup>63</sup>	Active control group (HA injection)
Karatosun, 2006 <sup>64</sup>	No intra-articular injection in control group
Kawasaki, 2009 <sup>65</sup>	No intra-articular injection in control group
Khanasuk, 2012 <sup>66</sup>	Sample size less than 30 in any group
Kianmehr, 2018 <sup>67</sup>	Active control group (HA injection)
Kirchner, 2006 <sup>68</sup>	Active control group (HA injection)
Kotevoglou, 2006 <sup>69</sup>	Sample size less than 30 in any group
Kul-Panza, 2010 <sup>70</sup>	Sample size less than 30 in any group
Lamo-Espinosa, 2016 <sup>71</sup>	Active control group (mesenchymal stromal cell injection)
Lamo-Espinosa, 2018 <sup>72</sup>	Active control group (mesenchymal stromal cell injection)
Leardini, 1987 <sup>73</sup>	Sample size less than 30 in any group
Leardini, 1991 <sup>74</sup>	Sample size less than 30 in any group
Leighton, 2014 <sup>75</sup>	Active control group (corticosteroid injection)
Leopold, 2003 <sup>76</sup>	Active control group (corticosteroid injection)
Lisi, 2018 <sup>77</sup>	Active control group (platelet-rich plasma injection)
Listrat, 1997 <sup>78</sup>	Patients underwent knee surgery
Louis, 2018 <sup>79</sup>	Active control group (platelet-rich plasma injection)
McDonald, 2000 <sup>80</sup>	Active control group (HA injection)
Miltner, 2002 <sup>81</sup>	Within-patient control
Navarro-Sarabia, 2011 <sup>82</sup>	Patients underwent multiple treatment cycles
Ozturk, 2006 <sup>83</sup>	Sample size less than 30 in any group
Pavelka, 2011 <sup>84</sup>	Active control group (HA injection)
Payne, 2000 <sup>85</sup>	Sample size less than 30 in any group
Pedersen, 1993 <sup>86</sup>	Sample size less than 30 in any group
Petrella, 2009 <sup>87</sup>	Sample size less than 30 in any group
Pham, 2004 <sup>88</sup>	Active control group (corticosteroid injection)
Raeissadat, 2018 <sup>89</sup>	Active control group (ozone injection)
Raman, 2008 <sup>90</sup>	Active control group (HA injection)
Raynauld, 2002 <sup>91</sup>	No intra-articular injection in control group
Raynauld, 2005 <sup>92</sup>	No intra-articular injection in control group
Renklitepe, 2000 <sup>93</sup>	Sample size less than 30 in any group

Román, 2000 <sup>94</sup>	Sample size less than 30 in any group
Sala, 1995 <sup>95</sup>	Sample size less than 30 in any group
Sanofi, 2009 <sup>96</sup>	Sample size less than 30 in any group
Scale, 1994 <sup>97</sup>	Sample size less than 30 in any group
Schauss, 2012 <sup>98</sup>	Oral supplementation
Schneider, 1997 <sup>99</sup>	Sample size less than 30 in any group
Seikagaku Corp., 2011 <sup>100</sup>	Redundant with Strand (2012)
Sezgin, 2005 <sup>101</sup>	Sample size less than 30 in any group
Shimizu, 2010 <sup>102</sup>	Sample size less than 30 in any group
Skwara, 2009 <sup>103</sup>	Sample size less than 30 in any group
Skwara, 2009 <sup>104</sup>	Active control group (corticosteroid injection)
Strand, 2016 <sup>105</sup>	Redundant with Strand (2012)
Su, 2018 <sup>106</sup>	Active control group (platelet-rich plasma injection)
Sun, 2017 <sup>107</sup>	Active control group (HA injection)
Suppan, 2017 <sup>108</sup>	Active control group (HA injection)
Tamir, 2001 <sup>109</sup>	Sample size less than 30 in any group
Tammachote, 2016 <sup>110</sup>	Active control group (corticosteroid injection)
Tasciotaoglu, 2003 <sup>111</sup>	Active control group (corticosteroid injection)
Tekeoglu, 1998 <sup>112</sup>	Sample size less than 30 in any group
Tetik, 2003 <sup>113</sup>	No intra-articular injection in control group
Toda, 2008 <sup>114</sup>	Sample size less than 30 in any group
Torrance, 2002 <sup>115</sup>	Redundant with Reynauld (2002)
Trueba Vasavilbaso, 2017 <sup>116</sup>	Patients underwent knee surgery
Tsai, 2003 <sup>117</sup>	No relevant outcomes reported
Vaishya, 2017 <sup>118</sup>	Active control group (corticosteroid injection)
Wang, 2018 <sup>119</sup>	Active control group (HA injection)
Wang, 2018 <sup>120</sup>	Sample size less than 30 in any group
Westrich, 2009 <sup>121</sup>	Patients underwent knee surgery
Wu, 2004 <sup>122</sup>	No relevant outcomes reported
Xin, 2016 <sup>123</sup>	Active control group (HA injection)
Yu, 2018 <sup>124</sup>	No relevant outcomes reported

**Supplement Table 3. Sensitivity Analysis of One-Study Removed Safety Results of Intra-articular Hyaluronic Acid for Knee Osteoarthritis.**

Event	No. Influential Studies <sup>a</sup>	Minimum RR <sup>b</sup>			Maximum RR <sup>b</sup>		
		RR	95% CI	P	RR	95% CI	P
<b>Adverse event</b>							
Any	0	1.00	0.95, 1.06	0.88	1.03	0.97, 1.08	0.38
Local	0	1.18	1.04, 1.34	0.01	1.28	1.11, 1.48	<0.001
Serious	0	1.35	0.83, 2.18	0.22	1.53	0.97, 2.42	0.07
<b>Study withdrawal</b>							
Any	0	0.95	0.83, 1.10	0.52	1.00	0.88, 1.14	>0.99
Adverse event-related	2 (9%)	1.27	0.88, 1.84	0.20	1.59	1.07, 2.37	0.02

<sup>a</sup>Indicates the number of studies in which removal of that study altered meta-analysis conclusions.

<sup>b</sup>Data derived from a one-study removed sensitivity analysis in which we iteratively removed one study at a time to determine whether conclusions were influenced by any single study. The minimum and maximum risk ratios (RR) demarcate the range of values derived from the analysis of each outcome. A RR>1 indicates higher risk with intra-articular hyaluronic acid. A RR<1 indicates lower risk with intra-articular hyaluronic acid.

**Supplement Table 4. Sensitivity Analysis of Fixed-Effect versus Random Effects Meta-analysis Models.**

Event	Heterogeneity (I <sup>2</sup> )	Fixed-Effect			Random Effects		
		RR <sup>a</sup>	95% CI	P	RR <sup>a</sup>	95% CI	P
<b>Adverse event</b>							
Any	0%	1.01	0.96, 1.07	0.61	1.01	0.96, 1.07	0.61
Local	9%	1.21	1.07, 1.36	0.003	1.23	1.07, 1.41	0.003
Serious	0%	1.44	0.91, 2.26	0.12	1.44	0.91, 2.26	0.12
<b>Study withdrawal</b>							
Any	0%	0.99	0.87, 1.12	0.83	0.99	0.87, 1.12	0.83
Adverse event-related	0%	1.37	0.97, 1.93	0.08	1.37	0.97, 1.93	0.08

<sup>a</sup>A risk ratio (RR) >1 indicates higher risk with intra-articular hyaluronic acid. A RR<1 indicates lower risk with intra-articular hyaluronic acid.

## Supplement References

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