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REVIEW ARTICLE

EFFICACY OF HYALURONIC ACID AFTER KNEE ARTHROSCOPY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objective: **To investigate the effect of hyaluronic acid on functional recovery and pain control in patients following knee arthroscopy.**
Design: **A systematic review and meta-analysis was conducted to explore the efficacy of hyaluronic acid following knee arthroscopy.**
Subjects and methods: **Randomized controlled trials (RCTs) assessing the effect of hyaluronic acid in knee arthroscopy were included. A meta-analysis was performed using the random-effect model.**
Results: **Six RCTs involving 310 patients were included in the meta-analysis. Overall, compared with control intervention following knee arthroscopy, hyaluronic acid treatment was found to significantly increase Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores (mean difference 11.43; 95% confidence intervals (95% CI) 1.39–21.47; $p = 0.03$), but had no impact on pain scores at 2 weeks (mean difference −0.16; 95% CI −0.81–0.49; $p = 0.63$), pain scores at 6 weeks (mean difference 0.01; 95% CI −0.86–0.89; $p = 0.98$), pain scores at 12 weeks (mean difference −0.51; 95% CI −1.56–0.53; $p = 0.34$). In addition, pain on motion was significantly reduced after knee arthroscopy (risk ratio (RR) 0.22; 95% CI 0.06–0.79; $p = 0.02$).**
Conclusion: Compared with control intervention after knee arthroscopy, hyaluronic acid treatment was found to significantly improve WOMAC score and decrease pain on motion, but had no substantial influence on pain scores at 2, 6 and 12 weeks after knee arthroscopy.

Key words: hyaluronic acid; knee arthroscopy; WOMAC score; viscosupplementation; meta-analysis.

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LAY ABSTRACT

Hyaluronic acid might be beneficial for patients after knee arthroscopy. However, the results remain controversial. A systematic review and meta-analysis was conducted to explore the efficacy of hyaluronic acid following knee arthroscopy. Randomized controlled trials assessing the effect of hyaluronic acid in knee arthroscopy were included. Compared with control intervention after knee arthroscopy, hyaluronic acid treatment was found to significantly improve Western Ontario and McMaster Universities Osteoarthritis Index scores and decrease pain on motion, but had no substantial influence on pain scores at 2, 6 and 12 weeks after knee arthroscopy.

In the short-term postoperative period after knee arthroscopy patients frequently experience pain, swelling and impaired function (1–3). Knee arthroscopy is widely used for anterior cruciate ligament reconstruction, meniscus tear, and arthroscopic debridement. Currently, several analgesics are used for pain control following arthroscopic knee surgery, resulting in some adverse events (4, 5). During knee arthroscopy, the normal hyperviscous synovial fluid is replaced by irrigation fluid (normal saline), which is further replaced by new, naturally formed synovial fluid after the surgery. The irrigation fluid not only facilitates the removal of harmful debris, but also dilutes the hyaluronic acid layer covering joint tissues (e.g. cartilage). Irrigation fluids have been reported to have a negative effect on the metabolism and structure of the joint cartilage (6–9).

Hyaluronic acid, a complex glycosaminoglycan, is an important component of synovial fluid and cartilage matrix, which lubricates and allows smooth and pain-free joint motion (10–12). Hyaluronic acid could promote homeostasis of the joint environment and serve as a semipermeable barrier to protect the cartilage from the free movement of lytic enzymes, inflammation mediators, and inflammatory cells in the synovial fluid (13–15). In addition, hyaluronic acid has been reported to relieve joint pain and prevent the progression of cartilage degeneration in osteoarthritis (16). Exogenous hyaluronic acid injected into the arthritic joint space has been shown to improve the qualitative and quantitative properties of endogenous hyaluronic acid and therefore improve joint lubrication (17). In a randomized controlled study (RCT), intra-articular hyaluronic acid was reported to improve pain control and swelling after arthroscopic anterior cruciate ligament reconstruction (18).

In contrast to this promising finding, however, some RCTs have shown that hyaluronic acid has no influence on Western Ontario and McMaster Universities

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Osteoarthritis Index (WOMAC) scores, and pain scores at 2 and 6 weeks following knee arthroscopy (19–21). Considering these inconsistent effects, we therefore conducted a systematic review and meta-analysis of RCTs to evaluate the effectiveness of hyaluronic acid after knee arthroscopy.

MATERIAL AND METHODS

This systematic review and meta-analysis was conducted according to the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (22) and the Cochrane Handbook for Systematic Reviews of Interventions (23). All analyses were based on previous published studies, thus ethical approval and patient consent were not required.

Literature search and selection criteria

PubMed, Embase, Web of Science, EBSCO, and the Cochrane Library were systematically searched from inception to September 2017, with the following key words: hyaluronic acid, and knee arthroscopy. To include additional eligible studies, the reference lists of retrieved studies and relevant reviews were also hand-searched and the process above was performed repeatedly until no further article was identified. Conference abstracts meeting the inclusion criteria were also included.

The inclusion criteria were: study population, patients undergoing knee arthroscopy; intervention, hyaluronic acid injection; control intervention, normal saline or no injection; outcome measure, WOMAC scores; and study design, RCT. Patients receiving local anaesthetic in the control group were excluded.

Data extraction and outcome measures

The following information was extracted for the included RCTs: first author, publication year, sample size, baseline characteristics of patients, hyaluronic acid, control, study design, WOMAC scores, pain scores at 2, 6 and 12 weeks, pain on motion. The author would be contacted to acquire the data when necessary.

The primary outcome was WOMAC score. Secondary outcomes included pain scores at 2, 6 and 12 weeks, pain on motion.

Quality assessment in individual studies

The Jadad scale was used to evaluate the methodological quality of each RCT included in this meta-analysis (24). This scale consisted of 3 evaluation elements: randomization (0–2 points), blinding (0–2 points), dropouts and withdrawals (0–1 points). One point would be allocated to each element if it was mentioned in article, and another 1 point would be given if the methods of randomization and/or blinding had been described appropriately and in detail. If methods of randomization and/or blinding were inappropriate, or dropouts and withdrawals had not been recorded, then 1 point was deducted. The Jadad scale score varied from 0 to 5 points. An article with Jadad score ≤ 2 was considered to be of low quality. If the Jadad score was ≥ 3, the study was thought to be of high quality (25). Two investigators independently assessed the quality of included studies. Any discrepancy should be solved by consensus.

Statistical analysis

Mean differences (MDs) with 95% confidence intervals (95% CIs) for continuous outcomes (WOMAC scores, pain scores at 2, 6 and 12 weeks) and risk ratios (RRs) with 95% CIs for dichotomous outcomes (pain on motion) were used to estimate the pooled effects. An I^2 value greater than 50% indicates significant heterogeneity. The random-effects model with DerSimonian and Laird weights was used in all analyses. Sensitivity analysis was performed to detect the influence of a single study on the overall estimate via omitting 1 study in turn when necessary. Owing to the limited number (<10) of included studies, publication bias was not assessed. $p<0.05$ in 2-tailed tests was considered statistically significant. All statistical analyses were performed with Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

RESULTS

Literature search, study characteristics and quality assessment

The flow chart for the selection process and detailed identification was presented in Fig. 1. A total of 678 publications were identified through the initial search of databases. Ultimately, 6 RCTs were included in the meta-analysis (18–21, 26, 27).

The baseline characteristics of the 6 eligible RCTs in the meta-analysis were summarized in Table I. The 6 studies were published between 2007 and 2012, and sample sizes ranged from 29 to 80, with a total of 310. There were similar characteristics between the hyaluronic acid group and the control group at baseline. One RCT reported knee arthroscopy for anterior cruciate ligament reconstruction (18), 2 RCTs reported knee arthroscopy for meniscus tear (26, 27), 2 RCTs reported arthroscopic debridement for knee osteoarthritis (19, 21), and 1 RCT reported arthroscopic knee joint lavage, or in combination with cartilage debridement (20).

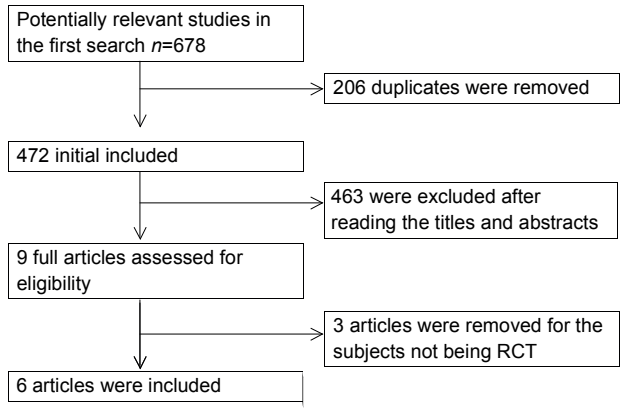

Fig. 1. Flow diagram of study searching and selection process.

Table I. Characteristics of included studies

Number	Author	Hyaluronic acid group: *n*	Age, years	Male, *n*	Weight (kg) or BMI (kg/m^2)	Methods	Control group: *n*	Age, years	Male, *n*	Weight (kg) or BMI (kg/m^2)	Methods	Surgery	Jada scores
1	Chau 2012	16	27±6	13	70±15 kg	10 ml of sodium hyaluronate 0.5% (Viscoseal®) through an arthroscopic portal with a cannula	16	26±7	15	70±7 kg	Normal saline	Anterior cruciate ligament reconstruction	5
2	Thein 2010	28	34 (17–44)	–	–	10 ml intra-articular Viscoseal®	28	34 (17–44)	–	–	Normal saline	Meniscus tear	3
3	Westrich 2009	23	59.3 (42–81)	–	29.0 (19.8–38.2) kg/m^2	First intra-articular sodium hyaluronate injection immediately after surgery, 10– 14 days later, and the final injection was given 17–21 days after surgery	23	59.3 (42–81)	–	29.0 (19.8–38.2) kg/m^2	No injection	Symptomatic meniscus tear	4
4	Heybeli 2008	33	56.7	12	–	Three intra-articular injections of 2 ml HA administered during 3 consecutive weeks starting 3-weeks postoperatively	34	54.4	9	–	No injection	Arthroscopic debridement for knee osteoarthritis	4
5	Atay 2008	14	53.4±5.0	–	31.7±5.1 kg/m^2	Five intra-articular injections of 2 ml sodium hyaluronate	15	53.1±6.9	–	27.5±5.3 kg/m^2	No injection	Arthroscopic debridement for knee osteoarthritis	4
6	Hempfling 2007	40	60.9±8.1	–	79.6±14.7 kg	Intra-articular instillation of 10 ml of the synovial fluid substitute (0.5% sodium hyaluronate)	40	60.9±8.1	–	79.6±14.7 kg	No injection	Arthroscopic knee joint lavage, or in combination with cartilage debridement	3

BMI: body mass index; HA: hyaluronic acid.

Among the 6 RCTs, 2 studies reported WOMAC scores (19, 21), 2 reported pain scores at 2 weeks (18, 20), 2 reported pain scores at 6 weeks (18, 21), 3 reported pain scores at 12 weeks (18, 21, 27), 2 reported pain on motion (20, 27). Jadad scores of the 6 included studies varied from 3 to 5, all 6 studies were considered to be high-quality ones according to quality assessment.

Primary outcome: WOMAC scores

This outcome data was analysed with a random-effects model, the pooled estimate of the 2 included RCTs suggested that, compared with the control group after knee arthroscopy, hyaluronic acid injection was associated with significantly increased WOMAC scores (mean difference = 11.43; 95% CI = 1.39 to 21.47; p = 0.03), with no heterogeneity among the studies (I^2 = 0%, heterogeneity p = 0.73) (Fig. 2).

Sensitivity analysis

No heterogeneity was observed among the included studies for the WOMAC scores. Thus, we did not perform sensitivity analysis by omitting 1 study in turn to detect the source of heterogeneity.

Secondary outcomes

Compared with control intervention following knee arthroscopy, hyaluronic acid had no substantial impact on pain scores at 2 weeks (MD –0.16; 95% CI –0.81–0.49; p = 0.63; Fig. 3a), 6 weeks (MD 0.01; 95% CI –0.86–0.89; p = 0.98; Fig. 3b), or 12 weeks (MD –0.51; 95% CI –1.56–0.53; p=0.34; Fig. 3c), but resulted in significantly reduced pain on motion (RR 0.22; 95% CI 0.06–0.79; p = 0.02; Fig. 4).

DISCUSSION

Pain management allowed early mobilization and rehabilitation following knee arthroscopy, and mainly included oral analgesics, femoral nerve block, and intra-articular injections (28–30). Continuous femoral nerve block was revealed to alleviate pain within 48 h, but had no influence on pain management and knee function (28, 31, 32). Intra-articular fentanyl/bupivacaine achieved comparable efficacy in relation to femoral nerve block in the first 24 h (33). Intra-articular injection of tenoxicam could reduce analgesic consumption in the first 3–6 h (34).

Exogenous hyaluronic acid was reported to stimulate de novo synthesis of hyaluronic acid, and inhibit the release of arachidonic acid and interleukin-1α-induced prostaglandin E_2 synthesis, which reduced the anti-

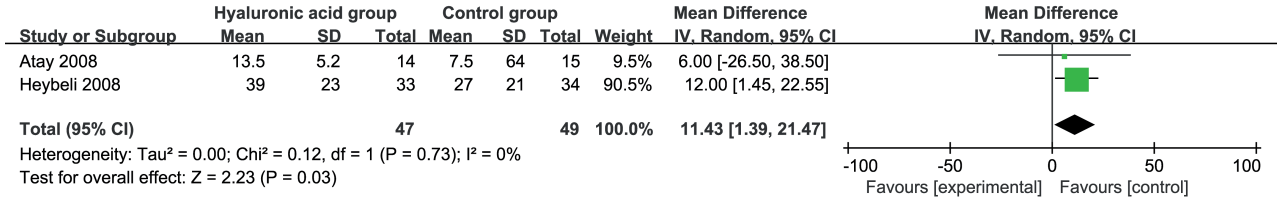

Fig. 2. Forest plot for the meta-analysis of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores.

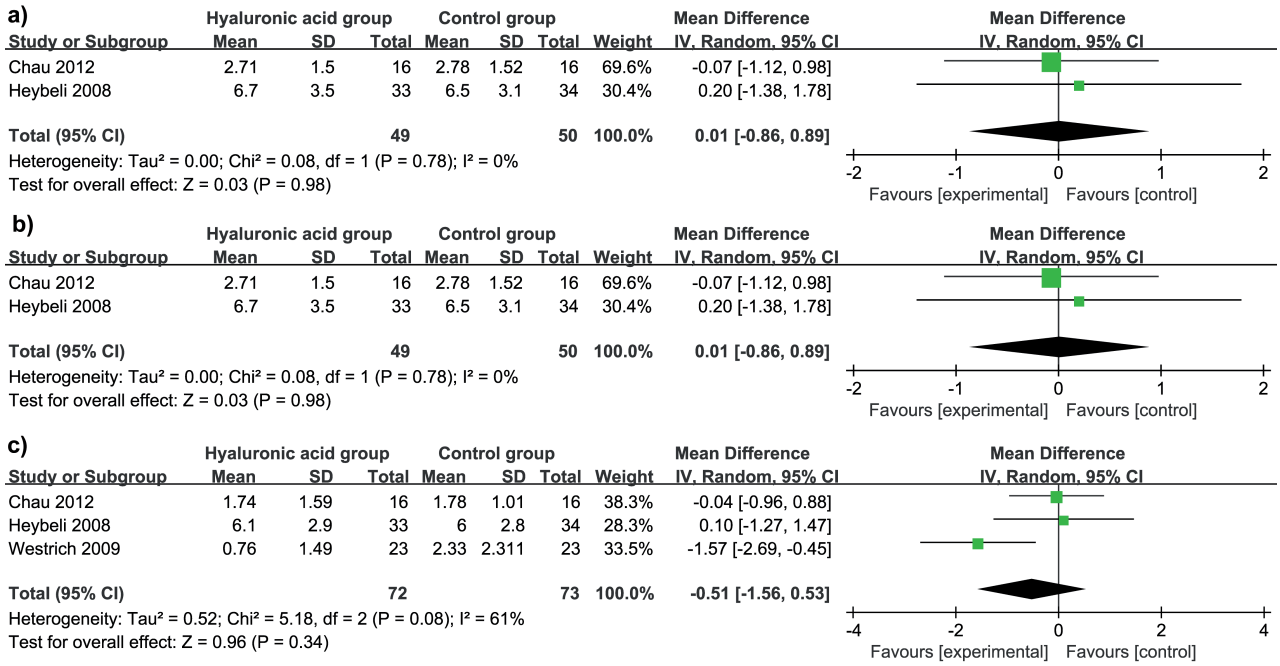

Fig. 3. Forest plot for the meta-analysis of pain scores at (a) 2 weeks, (b) 6 weeks and (c) 12 weeks.

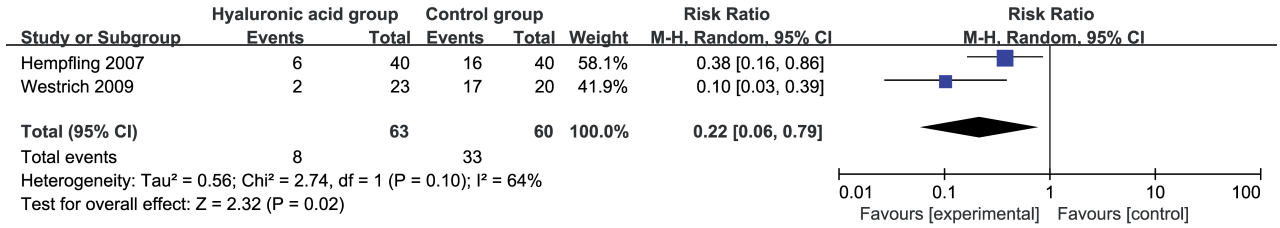

Fig. 4. Forest plot for the meta-analysis of pain on motion.

inflammatory response for pain control (35). One included RCT reported that hyaluronic acid treatment was capable of substantially alleviating pain and symptoms within 2 days after arthroscopic anterior cruciate ligament reconstruction (18). Another RCT also reported that statistically significant pain reduction was found 1 week postoperatively in arthroscopic surgery (26). In our meta-analysis, hyaluronic acid was revealed to significantly reduce pain on motion in knee arthroscopy, but had no influence on pain control 2, 6 and 12 weeks after the arthroscopic surgery. These results support the efficacy of hyaluronic acid treatment for pain control 1 week postoperatively when the inflammatory response after surgery is obvious.

Hyaluronic acid has been reported to result in a more rapid recovery from arthroscopic surgery, with less pain, less effusion, and a lower intake of analgesics (26). One RCT, involving 66 patients with various degrees of chondral damage, showed that post-arthroscopic instillation of hyaluronic acid-based synovial fluid substitute into the joint benefited long-term stabilization of treatment outcome 2 years after surgery (20). Another multicentre, prospective, open study showed that hyaluronic acid could provide effective pain relief,

and improve stiffness and physical function at 4–12 weeks after arthroscopic meniscectomy in patients with knee osteoarthritis (36). The current meta-analysis also indicated that hyaluronic acid was associated with significantly increased physical function, as evidenced by the improved WOMAC scores. The incidence of postoperative swelling was reported to be significantly reduced after hyaluronic acid injection following knee arthroscopy (27).

Several study limitations should be taken into account. Firstly, our analysis was based on only 6 RCTs, all of which have a relatively small sample size ($n < 100$). Overestimation of the treatment effect was more likely in smaller trials compared with larger samples. The detailed methods of knee arthroscopy, and the variation in timing and volume of hyaluronate in the included studies were different. These factors may have an influence on the pooling results. Next, the duration and follow-up time of hyaluronic acid varied from 2 weeks to 2 years. Finally, it was necessary to compare therapeutic effects of hyaluronic acid with femoral nerve block, intra-articular opioids and anti-inflammatory drugs.

CONCLUSION

Hyaluronic acid treatment showed important abilities to reduce pain on motion in the short-term and to improve physical function in knee arthroscopy.

The authors have no conflicts of interest to declare.

REFERENCES

1. Camp CL, Krych AJ, Stuart MJ, Regnier TD, Mills KM, Turner NS. Improving resident performance in knee arthroscopy: a prospective value assessment of simulators and cadaveric skills laboratories. J Bone Joint Surg Am 2016; 98: 220–225.
2. Ambrosoli AL, Chiaranda M, Fedele LL, Gemma M, Cedrati V, Cappelleri G. A randomised controlled trial of intrathecal blockade versus peripheral nerve blockade for day-case knee arthroscopy. Anaesthesia 2016; 71: 280–284.
3. Saltzman BM, Dave A, Young A, Ahuja M, Amin SD, Bush-Joseph CA. Prolonged epidural infusion improves functional outcomes following knee arthroscopy in patients with arthrofibrosis after total knee arthroplasty: a retrospective evaluation. J Knee Surg 2016; 29: 40–46.
4. Talu GK, Ozyalcin S, Koltka K, Erturk E, Akinci O, Asik M, et al. Comparison of efficacy of intraarticular application of tenoxicam, bupivacaine and tenoxicam: bupivacaine combination in arthroscopic knee surgery. Knee Surg Sports Traumatol Arthrosc 2002; 10: 355–360.
5. Gonzales J, Lovald ST, Lau EC, Ong KL. Quantifying the risk of analgesic-related adverse events after knee arthroscopy. J Surg Orthop Adv 2016; 25: 215–221.
6. Bulstra SK, Kuijer R, Eerdmans P, van der Linden AJ. The effect in vitro of irrigating solutions on intact rat articular cartilage. J Bone Joint Surg Br 1994; 76: 468–470.
7. Cuellar VG, Cuellar JM, Kirsch T, Strauss EJ. Correlation of synovial fluid biomarkers with cartilage pathology and associated outcomes in knee arthroscopy. Arthroscopy 2016; 32: 475–485.
8. Kohlhof H, Gravius S, Kohl S, Ahmad SS, Randau T, Schmolders J, et al. Single molecule microscopy reveals an increased hyaluronan diffusion rate in synovial fluid from knees affected by osteoarthritis. Sci Rep 2016; 6: 21616.
9. Bigoni M, Turati M, Sacerdote P, Gaddi D, Piatti M, Castelnuovo A, et al. Characterization of synovial fluid cytokine profiles in chronic meniscal tear of the knee. J Orthop Res 2017; 35: 340–346.
10. Temple-Wong MM, Ren S, Quach P, Hansen BC, Chen AC, Hasegawa A, et al. Hyaluronan concentration and size distribution in human knee synovial fluid: variations with age and cartilage degeneration. Arthritis Res Ther 2016; 18: 18.
11. Tamura T, Higuchi Y, Kitamura H, Murao N, Saitoh R, Morikawa T, et al. Novel hyaluronic acid-methotrexate conjugate suppresses joint inflammation in the rat knee: efficacy and safety evaluation in two rat arthritis models. Arthritis Res Ther 2016; 18: 79.
12. Russo F, D'Este M, Vadala G, Cattani C, Papalia R, Alini M, et al. Platelet rich plasma and hyaluronic acid blend for the treatment of osteoarthritis: rheological and biological evaluation. PloS One 2016; 11: e0157048.
13. Tehranzadeh J, Booya F, Root J. Cartilage metabolism in osteoarthritis and the influence of viscosupplementation and steroid: a review. Acta Radiol 2005; 46: 288–296.
14. Waddell DD, Bert JM. The use of hyaluronan after arthroscopic surgery of the knee. Arthroscopy 2010; 26: 105–111.
15. Maheu E, Rannou F, Reginster JY. Efficacy and safety of hyaluronic acid in the management of osteoarthritis: Evidence from real-life setting trials and surveys. Semin Arthritis Rheum 2016; 45: S28–S33.
16. Hashizume M, Koike N, Yoshida H, Suzuki M, Mihara M. High molecular weight hyaluronic acid relieved joint pain and prevented the progression of cartilage degeneration in a rabbit osteoarthritis model after onset of arthritis. Mod Rheumatol 2010; 20: 432–438.
17. Balazs EA, Denlinger JL. Viscosupplementation: a new concept in the treatment of osteoarthritis. J Rheumatol Suppl 1993; 39: 3–9.
18. Chau JY, Chan WL, Woo SB, Cheng SC, Wong TM, Wong TK, et al. Hyaluronic acid instillation following arthroscopic anterior cruciate ligament reconstruction: a double-blinded, randomised controlled study. J Orthop Surg 2012; 20: 162–165.
19. Atay T, Aslan A, Baydar ML, Ceylan B, Baykal B, Kirdemir V. The efficacy of low- and high-molecular-weight hyaluronic acid applications after arthroscopic debridement in patients with osteoarthritis of the knee. Acta Orthop Traumatol Turc 2008; 42: 228–233.
20. Hempfling H. Intra-articular hyaluronic acid after knee arthroscopy: a two-year study. Knee Surg Sports Traumatol Arthrosc 2007; 15: 537–546.
21. Heybeli N, Doral MN, Atay OA, Leblebicioglu G, Uzumcugil A. Intra-articular sodium hyaluronate injections after arthroscopic debridement for osteoarthritis of the knee: a prospective, randomized, controlled study. Acta Orthop Traumatol Turc 2008; 42: 221–227.
22. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339: b2535.
23. Higgins JPT GS. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration 2011.
24. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996; 17: 1–12.
25. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Ann Intern Med 2001; 135: 982–989.

26. Thein R, Haviv B, Kidron A, Bronak S. Intra-articular injection of hyaluronic acid following arthroscopic partial meniscectomy of the knee. Orthopedics 2010; 33: 724.
27. Westrich G, Schaefer S, Walcott-Sapp S, Lyman S. Randomized prospective evaluation of adjuvant hyaluronic acid therapy administered after knee arthroscopy. Am J Orthop 2009; 38: 612–616.
28. Williams BA, Kentor ML, Vogt MT, Irrgang JJ, Bottegal MT, West RV, et al. Reduction of verbal pain scores after anterior cruciate ligament reconstruction with 2-day continuous femoral nerve block: a randomized clinical trial. Anesthesiology 2006; 104: 315–327.
29. Dauri M, Polzoni M, Fabbi E, Sidiropoulou T, Servetti S, Coniglione F, et al. Comparison of epidural, continuous femoral block and intraarticular analgesia after anterior cruciate ligament reconstruction. Acta Anaesthesiol Scand 2003; 47: 20–25.
30. Brignardello-Petersen R, Guyatt GH, Buchbinder R, Poolman RW, Schandelmaier S, Chang Y, et al. Knee arthroscopy versus conservative management in patients with degenerative knee disease: a systematic review. BMJ Open 2017; 7: e016114.
31. Reuben SS, Sklar J. Preemptive multimodal analgesia for anterior cruciate ligament surgery. Reg Anesth Pain Med 2002; 27: 225; author reply 225–226.
32. Wulf H, Lowe J, Gnutzmann KH, Steinfeldt T. Femoral nerve block with ropivacaine or bupivacaine in day case anterior crucial ligament reconstruction. Acta Anaesthesiol Scand 2010; 54: 414–420.
33. Mayr HO, Entholzner E, Hube R, Hein W, Weig TG. Pre- versus postoperative intraarticular application of local anesthetics and opioids versus femoral nerve block in anterior cruciate ligament repair. Arch Orthop Trauma Surg 2007; 127: 241–244.
34. Guler G, Karaoglu S, Velibasoglu H, Ramazanogullari N, Boyaci A. Comparison of analgesic effects of intra-articular tenoxicam and morphine in anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 2002; 10: 229–232.
35. Jackson DW, Scheer MJ, Simon TM. Cartilage substitutes: overview of basic science and treatment options. J Am Acad Orthop Surg 2001; 9: 37–52.
36. Huskin JP, Vandekerckhove B, Delince P, Verdonk R, Dubuc JE, Willems S, et al. Multicentre, prospective, open study to evaluate the safety and efficacy of hylan G-F 20 in knee osteoarthritis subjects presenting with pain following arthroscopic meniscectomy. Knee Surg Sports Traumatol Arthrosc 2008; 16: 747–752.