คู่มือ

และ

รายงานความเห็นร่วม

ของศัลยแพทย์ออร์โธปิดิกส์ประเทศไทย

เรื่อง **การใช้ยารักษาข้อเข่าเสื่อม**

ประเทศไทย พ.ศ.2562

Manual and Proceedings of
the Thai Consensus Conference
on Pharmacological Management
of Knee OA 2019

โดย

ชมรมศัลยแพทย์ข้อสะโพกข้อเข่าประเทศไทย
Thai Hip and Knee Society

คู่มือและรายงานความเห็นร่วม
ของศัลยแพทย์ออร์โธปิดิกส์ประเทศไทย

เรื่อง

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คำนิยมโดยประธานราชวิทยาลัย แพทย์ออร์โธปิดิกส์แห่งประเทศไทย

ในปี พ.ศ. 2559 ผมและคณะได้มีโอกาสริเริ่มการจัดประชุมสัมมนาให้เกิดข้อสรุปความเห็นร่วม (concensus meeting) สำหรับวงการวิชาชีพออร์โธปิดิกส์ขึ้นเป็นครั้งแรกในประเทศไทย โดยครั้งนั้นเป็นการหาความเห็นร่วมในการผ่าตัดรักษาโรคข้อเข่าเสื่อม โดยเฉพาะอย่างยิ่งการผ่าตัดเปลี่ยนข้อเข่าเทียม เพื่อทำให้เกิดแนวทางการรักษาที่เป็นประโยชน์ต่อผู้ป่วยสูงสุด และเป็นแนวทางปฏิบัติสำหรับแพทย์ออร์โธปิดิกส์ส่วนใหญ่ของประเทศ โดยอาศัยการรวบรวมเอกสารวิชาการบวกกับความเห็นของแพทย์ส่วนใหญ่กลุ่มหนึ่งที่เป็นผู้ชำนาญและมีประสบการณ์สูงในเรื่องเหล่านี้ เกิดข้อสรุปความเห็นร่วมในแต่ละประเด็นย่อย อันก่อให้เกิดความชัดเจนกับแพทย์ส่วนใหญ่ทั้งประเทศไทยในประเด็นการวินิจฉัย ข้อบ่งชี้การผ่าตัด มาตรฐานการผ่าตัด การดูแลผู้ป่วยก่อนและหลังการผ่าตัด การบันทึกข้อมูลผู้ป่วย ตลอดจนถึงชนิดของข้อเทียมที่เหมาะสม จนทำให้สำนักงานประกันสุขภาพแห่งชาติเห็นว่าข้อสรุปนี้มีประโยชน์และนำข้อสรุปนี้มาใช้เป็นแนวทางปรับปรุงการเบิกจ่ายชดเชยค่าใช้จ่ายคืนให้กับสถานพยาบาลในเวลาต่อมา

ในโอกาสที่ชมรมศัลยแพทย์ข้อสะโพกข้อเข่าประเทศไทย ซึ่งนำโดย พล.ต.ต. นพ.วิโรจน์ ลาภไพบูลย์พงศ์ และคณะ ได้เล็งเห็นความสำคัญในเรื่องความหลากหลายของการรักษาโรคที่พบบ่อยทางออร์โธปิดิกส์ โดยเฉพาะเรื่องการรักษาทางยาในผู้ป่วยที่เป็นโรคข้อเข่าเสื่อมจนกระทั่งหาข้อสรุปได้ยากบางกรณีย่อยของการรักษา ดังนั้น กิจกรรมของชมรมฯในครั้งนี้ คือ การหาข้อสรุปความเห็นร่วมในการดูแลรักษาผู้ป่วยโรคข้อเข่าเสื่อมโดยวิธีใช้ยาในปี ค.ศ. 2019 โดยเป็นการระดมข้อมูลวิชาการและความเห็นในเรื่องการรักษาทางยาสำหรับผู้ป่วยโรคข้อเข่าเสื่อมจากผู้เชี่ยวชาญแต่ละท่านที่มีความเห็น

ทั้งเหมือนกันและแตกต่างกันอย่างมากๆ นำมาอภิปรายหาความเห็นร่วมเพื่อทำให้เกิดข้อสรุปที่เป็นประโยชน์อย่างยิ่ง คือ ทำให้เกิดแนวทางปฏิบัติสำหรับแพทย์ออร์โธปิดิกส์ส่วนใหญ่ของประเทศ ดังนั้น ผมถือว่าเป็นเรื่องที่ดีอย่างยิ่งที่กิจกรรมนี้สมควรได้รับการสนับสนุนและยกย่องจากองค์กรวิชาชีพหลัก คือ ราชวิทยาลัยแพทย์ออร์โธปิดิกส์แห่งประเทศไทยนั่นเอง

ผมขอแสดงความชื่นชมในการร่วมมือร่วมใจกันของคณะทำงานกิจกรรมนี้ของชมรมศัลยแพทย์ข้อสะโพกข้อเข่าแห่งประเทศไทย และผู้เชี่ยวชาญทุกๆ ท่านที่เข้าร่วมกิจกรรมครั้งนี้ จนทำให้กิจกรรมสำเร็จลุล่วงไปได้อย่างสมบูรณ์และจนกระทั่งสามารถจัดพิมพ์เป็นรูปเล่ม โดยพิมพ์เนื้อหาแทบทั้งหมดเป็นภาษาอังกฤษ อันเป็นประโยชน์ไม่ใช่เพียงแต่ใช้อ้างอิงภายในประเทศไทย แต่ยังเผยแพร่ไปยังประเทศต่างๆ ในภูมิภาคอาเซียนด้วย ทั้งนี้ การได้รับความสำเร็จเป็นอย่างดีนี้ อนึ่ง ผมขอแสดงความชื่นชมเป็นพิเศษต่อหัวหน้าคณะทำงานครั้งนี้ คือ รศ. นพ.สาธิต เที่ยงวิทยาพร, น.อ. นพ.ธนา นรินทร์สรศักดิ์ และ พ.ท. นพ.สารเดช เชื่องศิริกุล และทีมงานย่อยของทั้งสามท่านที่สละทั้งเวลา แรงกาย และแรงใจ เป็นอย่างมาก ตั้งแต่ขั้นตอนการเตรียมการก่อนการจัดประชุม ขณะการจัดประชุม สรุปการจัดประชุม และการจัดเตรียมเรียบเรียงเนื้อหาทั้งหมดให้เป็นเอกสารวิชาการและจัดพิมพ์จนแล้วเสร็จ

ศาสตราจารย์นายแพทย์อารี ตนาวลี
ประธานราชวิทยาลัยแพทย์ออร์โธปิดิกส์แห่งประเทศไทย

คำนิยมโดยรองประธานราชวิทยาลัย แพทย์ออร์โธปิดิกส์แห่งประเทศไทย

ในฐานะรองประธานราชวิทยาลัยแพทย์ออร์โธปิดิกส์แห่งประเทศไทย ฝ่ายวิชาการ ผมขอชื่นชมในความตั้งใจจริงอย่างต่อเนื่องในการที่จะพัฒนาองค์ความรู้ในการรักษาโรคข้อเข่าเสื่อม ให้เป็นข้อสรุปเดียวกันมาอย่างต่อเนื่อง โดยมีหลักฐานเชิงประจักษ์ที่ชัดเจนจนออกมาเป็นหนังสือ Thai Consensus Conference on Pharmacological Management of Knee OA 2019 การที่จะรวบรวมความคิดเห็นจากแพทย์ผู้เชี่ยวชาญจำนวนมากในแต่ละสาขาที่เกี่ยวข้องกับการรักษาโรคข้อเข่าเสื่อม เป็นเรื่องที่ไม่ง่าย แต่ภายใต้การทำงานของประธานการประชุม Thai Consensus Conference on Pharmacological Management of Knee OA 2019 ของ พล.ต.ต. นพ.วิโรจน์ ลาภไพบูลย์พงศ์ ได้พิสูจน์ให้เห็นแล้วว่า ทำได้จริง ประสบความสำเร็จอย่างน่าภูมิใจเป็นอย่างยิ่ง ทั้งในเรื่องของจำนวนแพทย์ที่เข้าร่วม ขบวนการขั้นตอนของการดำเนินการ รวมถึงผลสรุปที่ออกมา ความรู้ที่ได้มาในครั้งนี้ นับว่ามีประโยชน์อย่างมากสำหรับแพทย์ทุกท่าน ที่ดูแลผู้ป่วยโรคข้อเข่าเสื่อมโดยการใช้ยา สามารถนำไปเป็นแนวทางในการใช้เพื่อรักษาคนไข้ข้อเข่าเสื่อม อย่างมีประสิทธิภาพและนับเป็นข้อตกลงร่วมกันของประเทศไทย

ผมขอขอบคุณ รศ. นพ.สาธิต เที่ยงวิทยาพร เลขาการจัดสัมมนา ที่ทำหน้าที่อย่างเข้มแข็ง ตลอดจนหัวหน้าคณะทำงานทั้งสองกลุ่ม ได้แก่ น.อ. นพ.ธนา นรินทร์สรศักดิ์ และ พ.ท. นพ.สารเดช เชื่องศิริกุล รวมถึงผู้เข้าร่วมประชุมทุกท่าน ที่ได้เสียสละเวลาอันมีค่ามาร่วมกันแสดงความคิดเห็นในการประชุมครั้งนี้

รองศาสตราจารย์นายแพทย์ทิพชาติ บุณยรัตพันธุ์
รองประธานราชวิทยาลัยแพทย์ออร์โธปิดิกส์แห่งประเทศไทย
ฝ่ายวิชาการ

คำนิยมโดยประธานชมรมศัลยแพทย์ข้อสะโพกข้อเข่าประเทศไทย

ในปัจจุบัน การรักษาโรคข้อเสื่อมด้วยการผ่าตัดมีการพัฒนาไปอย่างต่อเนื่อง ทั้งด้านการผ่าตัดรักษาที่ได้ผลการรักษาดีมาก เช่น การผ่าตัดเปลี่ยนข้อเทียมครึ่งข้อหรือเต็มข้อ การผ่าตัดจัดแนวกระดูกเข่า การผ่าตัดเข่าผ่านกล้อง ซึ่งมีรายละเอียดต่างๆมาก ต้องอาศัยศัลยแพทย์ออร์โธปิดิกส์ที่เชี่ยวชาญด้านนี้รักษา อย่างไรก็ตามในด้านการรักษาโดยไม่ผ่าตัด ก็มีการพัฒนาไปอย่างมากเช่นกัน ทั้งประเภทยา ความหลากหลายของยาต่างๆมีออกมาให้เลือกอย่างมากมาย มีทั้งยารับประทาน ยาฉีด ยาทา หลายประเภท ทำให้เกิดการรักษาแบบไม่ผ่าตัดที่หลากหลายมาก รวมถึงมีความเข้าใจผิดในหลายๆประเด็นเช่นกัน

แม้ว่าจะมีการรายงานผลงานวิจัยเรื่องการรักษาโรคข้อเสื่อมด้วยวิธีการไม่ผ่าตัดอย่างมากมาย ซึ่งตีพิมพ์ทั้งในวารสารระดับชาติและระดับนานาชาติ แต่เห็นได้ว่ามีความหลากหลายทางความคิดเห็นของวิธีการรักษา ข้อบ่งชี้ ข้อห้าม วิธีการเลือกใช้ที่เหมาะสม ระยะเวลาในการติดตามการรักษาที่เหมาะสมและไม่เป็นอันตรายต่อผู้ป่วย เนื้อหาในผลงานวิจัยไม่ได้สะท้อนให้เห็นถึงความเหมาะสม ในการใช้ทรัพยากรทางการแพทย์ในประเทศไทยและประชากรไทย ทั้งนี้ในปัจจุบัน ยังไม่มีความตกลงกันในแนวทางการปฏิบัติการรักษาข้อเข่าเสื่อมโดยไม่ผ่าตัดแบบเดียวกัน ทำให้ผลการรักษาแตกต่างกัน ถึงแม้ว่าจะเป็นการดูแลผู้ป่วยในมาตรฐานเดียวกัน เพื่อให้ความหลากหลายในความคิดของบุคลากรทางการแพทย์และผู้เกี่ยวข้อง ซึ่งเกิดจากการอ้างอิง ความเข้าใจพื้นฐาน ประสบการณ์ในการรักษาแตกต่างกัน สามารถปรับเข้าหากันบนพื้นฐานของการประมวลองค์ความรู้ การใช้วิทยาศาสตร์เข้ามาพิสูจน์ การใช้สถิติที่ดีและน่าเชื่อถือ โดยมีหลักฐานที่แน่นหนาสนับสนุน เป็นแนวทางปฏิบัติร่วมกันและเป็นที่ร่วมรับทุกภาคส่วนในสังคม

เพื่อให้การรักษาโรคข้อเข่าเสื่อมด้วยการวิธีการไม่ผ่าตัดมีการเปลี่ยนแปลงไปในแนวทางที่เป็นประโยชน์ มีมาตรฐาน ปลอดภัย และสามารถใช้ได้เป็นวิธีการรักษาอย่างเหมาะสมก่อนตัดสินใจผ่าตัดเวลาที่เหมาะสม จึงมีความจำเป็นที่ต้องจัดประชุมเพื่อทำความเห็นร่วมในวิธีการรักษาข้อเข่าเสื่อมโดยไม่ผ่าตัด มาจากความเห็นของผู้เชี่ยวชาญที่ปฏิบัติจริงในประเทศไทย ทุกสาขาการแพทย์ที่เกี่ยวข้อง ได้แก่ ออร์โธปิดิกส์ อายุรกรรม เวชศาสตร์ครอบครัว กายภาพบำบัด จัดเป็นการประชุมความเห็นร่วม Thai Consensus Conference on Pharmacological Management of Knee OA 2019 โดยการดำเนินการความเห็นร่วมจะให้วิธีที่มาตรฐาน คือ วิธี modified Delphi เพื่อนำความแตกต่างในมุมมองของแพทย์ทุกสาขาที่เกี่ยวข้อง และจากภาคส่วนของประเทศไทย มาขัดเกลาจนเกิดฉันทามติในฐานะแพทย์ผู้ให้บริการดูแลผู้ป่วยที่เป็นข้อเข่าเสื่อม และยังไม่พร้อมที่จะรักษาโดยการผ่าตัดเปลี่ยนข้อเข่าเทียม จึงถือว่าเป็นบริบทที่มีประโยชน์อย่างมากแก่ประชาชนชาวไทยและอนาคตของประเทศไทย และเป็นแนวทางการวางแผนฐานข้อมูลที่ประโยชน์ของชาติด้านการสาธารณสุขต่อไป ในการนี้ทางชมรมศัลยแพทย์ข้อสะโพกข้อเข่าประเทศไทยยังได้รับเกียรติจากทางประธานและกรรมการราชวิทยาลัยแพทย์ออร์โธปิดิกส์แห่งประเทศไทย ส่งตัวแทนเข้าร่วมสังเกตการณ์ด้วย แสดงให้เห็นถึงกิจกรรมนี้อาจจะมีประโยชน์ในด้านอื่นๆ ด้วยนอกเหนือจากมาตรฐานการดูแลรักษาผู้ป่วย

ผมขอขอบคุณ รองศาสตราจารย์ นพ.สาธิต เที่ยงวิทยาพร, น.อ. นพ.ธนา นรินทร์สรศักดิ์, พ.ท. นพ.สารเดช เชื่องศิริกุล, พ.ต.ท. นพ.อุกฤษณ์ ฉวีวรรณากร, อ. นพ.ชวนนท์ สุมนะเศรษฐกุล และคณะกรรมการ ผู้เชี่ยวชาญจากสาขาต่างๆ แพทย์ที่ปรึกษา รวมถึงทีมเลขาฯ และผู้เกี่ยวข้องทุกคนที่กล่าวไม่หมด ที่ได้จัดทำ Thai Consensus Conference on Pharmacological Management of Knee OA 2019 ซึ่งต้องเสียสละเวลาอันมีค่า และทุ่มเทกำลังกายและใจ ทบทวน เตรียมการ ข้อมูลวิชาการที่สามารถนำไปปฏิบัติได้

จริง และที่เป็นยอมรับในกลุ่มแพทย์ทุกสาขาในการดูแลรักษาข้อเข่าเสื่อมโดยไม่ผ่าตัด ขอให้ประสบผลสำเร็จตามที่ทุกท่านได้ตั้งใจทุ่มเทลงไปทุกประการ

พลตำรวจตรีนายแพทย์วิโรจน์ ลาภไพบูลย์พงศ์
แพทย์ออร์โธปิดิกส์ผู้เชี่ยวชาญด้านการรักษาข้อสะโพกและข้อเข่า
ประธานชมรมศัลยแพทย์ข้อสะโพกข้อเข่าประเทศไทย
ประธานการจัดสัมมนา

คำนำ

ปัจจุบันประเทศไทยได้ก้าวเข้าสู่สังคมสูงอายุ เป้าหมายสำคัญของการรักษาโรคที่เกี่ยวกับผู้สูงอายุ คือ การรักษาที่ช่วยส่งเสริมคุณภาพการใช้ชีวิตของผู้สูงอายุให้ดีขึ้น และสามารถใช้ชีวิตประจำวันได้ตามปกติ โรคข้อเข่าเสื่อมเป็นโรคที่มีความสำคัญมากในกลุ่มผู้สูงอายุ และเป็นโรคที่แพทย์ออร์โธปิดิกส์ต้องดูแลรักษาผู้ป่วยเป็นจำนวนมาก ด้วยวิธีประคับประคองและการใช้ยานอกเหนือจากการผ่าตัด แม้ว่ามีการรายงานความก้าวหน้าของผลงานวิจัยเรื่องการรักษาโรคข้อเสื่อมด้วยยาจำนวนมากมาย ที่ตีพิมพ์ทั้งในวารสารระดับชาติและระดับนานาชาติ รวมถึงมีความหลากหลายทางความคิดเห็นของวิธีการใช้ยา อย่างไรก็ตามเนื้อหาที่พบในวารสารดังกล่าวไม่ได้ครอบคลุมถึงบริบทการใช้ยาทางการแพทย์สำหรับประเทศไทยและประชากรไทยได้อย่างเหมาะสม ชมรมศัลยแพทย์ข้อสะโพกข้อเข่าประเทศไทยได้เล็งเห็นถึงความจำเป็นที่ต้องสร้างมาตรฐานอันเป็นที่ได้รับการยอมรับของกลุ่มแพทย์ออร์โธปิดิกส์ที่ทำงานด้านนี้ รวมถึงแนวทางความเห็นร่วมในการรักษาโรคด้วยการใช้ยาให้มีประสิทธิภาพ เพื่อผลการรักษาที่ดีที่สุดต่อผู้ป่วย

ชมรมศัลยแพทย์ข้อสะโพกข้อเข่าประเทศไทยภายใต้การนำของ พล.ต.ต. นพ.วิโรจน์ ลาภไพบูลย์พงศ์ ได้ดำเนินการจัดสัมมนาเพื่อหาความเห็นร่วมของแพทย์ผู้เชี่ยวชาญเกี่ยวกับการใช้ยาในการดูแลรักษาป่วยโรคข้อเข่าเสื่อมโดยวิธี modified Delphi (Thai Consensus Conference on Pharmacological Management of Knee OA 2019) ที่โรงแรม Verona at Tablan ปราจีนบุรี เมื่อวันที่ 31 มกราคม และ 1 กุมภาพันธ์ 2562 ในงานประชุมครั้งนี้มีแพทย์เข้าร่วมให้ความเห็นในฐานะผู้เชี่ยวชาญประกอบไปด้วยทั้งแพทย์ออร์โธปิดิกส์ และแพทย์เวชศาสตร์ฟื้นฟูจำนวน 69 ท่าน

โดยได้แบ่งกลุ่มให้ความเห็นร่วมเป็น 2 กลุ่มหลักคือ กลุ่มที่ 1 ยารักษาข้อเข่าเสื่อมชนิดรับประทาน (oral medications for osteoarthritis of the knee) นำทีมโดย น.อ. นพ.ธนา นรินทร์สรศักดิ์ และกลุ่มที่ 2 ยารักษาข้อเข่าเสื่อมชนิดฉีดเข้าข้อและใช้ภายนอก (non-oral and topical medications for osteoarthritis of the knee) นำทีมโดย พ.ท. นพ.สารเดช เชื่องศิริกุล กระบวนการออกเสียงให้ความเห็นของผู้เชี่ยวชาญแต่ละท่านทำโดยอิสระผ่านระบบอิเล็กทรอนิกส์ โดยใช้ซอฟแวร์เฉพาะเพื่อหาความเห็นร่วมโดยวิธี modified Delphi ผู้เชี่ยวชาญแต่ละท่านสามารถให้ความเห็นเป็น เห็นด้วย (agree) หรือไม่เห็นด้วย (disagree) หรือไม่ออกเสียง (abstain) ระบบจะรวบรวมเสียงผู้เชี่ยวชาญทั้งหมดแล้วคำนวณร้อยละของผู้เห็นด้วยกับความเห็นร่วมในแต่ละข้อ โดยมีเกณฑ์ตัดสินระดับความเห็นดังนี้ 1) Simple Majority: No Consensus (50.1-59% agreement), 2) Majority: Weak Consensus (60-65% agreement), 3) Super Majority: Strong Consensus (66-99% agreement) และ 4) Unanimous: 100% agreement โดยในการสัมมนาครั้งนี้ได้ให้ความเห็นร่วมออกมาทั้งหมด 51 ข้อ ในจำนวนนี้มีความเห็น No Consensus จำนวน 1 ข้อ Weak Consensus จำนวน 1 ข้อ Strong Consensus จำนวน 43 ข้อ และ Unanimous จำนวน 6 ข้อ

ในโอกาสนี้ กระผมและคณะทำงานจัดการสัมมนาทุกท่านขอขอบคุณผู้ให้เกียรติเข้าร่วมสังเกตการณ์จากทางราชวิทยาลัยแพทย์ออร์โธปิดิกส์แห่งประเทศไทย ศ. นพ.อารี ตนาวลี ประธานราชวิทยาลัยแพทย์ออร์โธปิดิกส์แห่งประเทศไทย, ศ. นพ.ธไนนิธย์ โชตนภูติ ประธานรับเลือกราชวิทยาลัยแพทย์ออร์โธปิดิกส์แห่งประเทศไทย, นพ.ชาลี สุเมธวาณิชย์, นพ.อภิสิทธิ์ ปัทมารัตน์, ผศ. นพ.สีหธัช งามอุโฆษ, ผศ. นพ.ศิวดล วงค์ศักดิ์ ที่กรุณาสละเวลามากล่าวเปิดงานและร่วมสังเกตการณ์การสัมมนา ขอบคุณ พ.ต.ท.หญิง ละอองเทียน แสงสุข ในฐานะเลขานุการของการจัดสัมมนา คณะทำงานทุกท่านที่ทำงานด้านสนับสนุนอย่างเต็มกำลัง ขอบคุณ น.อ. นพ.ธนา นรินทร์สรศักดิ์ พ.ท. นพ.สารเดช เชื่องศิริกุลในฐานะผู้นำกลุ่มสัมมนา

ที่ทำงานหนัก ขอบคุณกองบรรณาธิการ ที่จัดทำคำอธิบายการให้ความเห็นร่วม (justification) และร่วมกันทำให้การจัดพิมพ์แล้วเสร็จทันกำหนด และขอขอบคุณอย่างยิ่งต่อแพทย์ออร์โธปิดิกส์ และแพทย์เวชศาสตร์ฟื้นฟูทุกท่านที่เข้าร่วมการสัมมนาและจัดทำความเห็นร่วมในครั้งนี้ จนทำให้งานสำเร็จได้เป็นอย่างดี กระผมหวังเป็นอย่างยิ่งว่าหนังสือคู่มือความเห็นร่วมการใช้ยาในการดูแลรักษาผู้ป่วยโรคข้อเข่าเสื่อมเล่มนี้ จะเป็นประโยชน์ต่อแพทย์ผู้รักษาโรคข้อเข่าเสื่อมในประเทศไทยทุกท่าน และช่วยส่งเสริมการใช้ยาทางการแพทย์เกี่ยวกับโรคข้อเข่าเสื่อมสำหรับประเทศไทยได้อย่างเหมาะสม ซึ่งผลโดยรวมก็จะได้ประโยชน์ต่อผู้ป่วยและการพัฒนาสาธารณสุขของประเทศไทยของเราต่อไป

รองศาสตราจารย์นายแพทย์สาธิต เที่ยงวิทยาพร
บรรณาธิการ
เลขาการจัดสัมมนา

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คณะกรรมการจัดงานสัมมนาเพื่อหาความเห็นร่วม การใช้ยารักษาข้อเข่าเสื่อมประเทศไทย พ.ศ. 2562
Committee of Thai Consensus Conference on Pharmacological Management of Knee Osteoarthritis 2019

ประธานจัดการประชุม (Chairman)

พลตำรวจตรีนายแพทย์วิโรจน์ ลาภไพบูลย์พงศ์

Police General Major Dr. Viroj Larbpaiboonpong

เลขาการจัดประชุม (Secretary General)

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ยารักษาข้อเข่าเสื่อมชนิดรับประทาน
Oral medications for osteoarthritis of the knee

รายชื่อกลุ่ม 1
ยารักษาข้อเข่าเสื่อมชนิดรับประทาน
Oral medications for osteoarthritis of the knee

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Session 1: ยารักษาข้อเข่าเสื่อมชนิดรับประทาน
Oral medications for osteoarthritis of the knee

คำถามที่ 1: กลุ่มยารับประทานที่เหมาะสมในการใช้รักษาข้อเข่าเสื่อมคือ

- Acetaminophen
- Opioids
- Non-steroidal anti-inflammatory drugs (NSAIDs); COX-1 inhibitors and COX-2 inhibitors
- Glucosamine sulphate
- Diacerein
- Pregabalin
- Muscle relaxants
- Duloxetine

Question 1: Oral medications for conservative treatment in osteoarthritis (OA) of the knee include:

- Acetaminophen
- Opioids
- Non-steroidal anti-inflammatory drugs (NSAIDs); COX-1 inhibitors and COX-2 inhibitors
- Glucosamine sulphate
- Diacerein
- Pregabalin
- Muscle relaxants
- Duloxetine

ความเห็นร่วม: ใช่
Consensus: Yes

Delegate vote: Agree 98.55%, Disagree 1.45%, Abstain 0% (Strong Consensus)

Justification: Osteoarthritis (OA) is one of the most common joint diseases, affecting 250 million people worldwide.[1] With an increasing aging population with longer life expectancies, the prevalence of this degenerative and progressive arthritis is expected to increase dramatically in the near future. An estimated 10% of men and 18% of women older than 60 years old are expected to develop symptomatic OA.[2] By the year 2020, OA is expected to be the fourth leading cause of disabilities worldwide.[3] Therefore, disabilities and functional impairments caused by this disease will lead to global negative socioeconomic effects.

Currently, OA is not considered as a sole pathology only involving articular cartilage, but rather as a disease of the whole joint, including the subchondral bone, capsule, ligaments, periarticular muscles, and the synovial membrane. It was a long believed that OA was an exclusively degenerative disease. However, recent studies have revealed that inflammation plays an important role in the pathogenesis and progression of OA.[4,5] Currently, the role of inflammation in OA is characterized as being low-grade and chronic, and not well-understood in comparison to inflammatory arthritis.

Based on their neurobiological mechanisms, the pathogenesis of OA pain can be categorized into three types: 1) nociceptive; 2) inflammatory; and 3) neuropathic pain.[6] Being able to recognize the different types of OA pain is important in determining the correct path of pharmacological treatment for patients. Abnormal loading on damaged articular cartilage causes alterations in the joint's biomechanics that results in the activity of mechano-gated ion channels expressed in nociceptive receptors, triggering the generation of classical pain.[7] As a sequela of OA leads to the breakdown of cartilage, nerve

endings from the subchondral bone become exposed to the intra-articular environment that is filled with various types of inflammatory mediators.[8] Sensory nerves in the surrounding soft tissues, such as in the menisci and synovium, also interact with pro-algesic mediators. This process leads to the generation of inflammatory pain common in osteoarthritic pain. Although, the etiology of nerve damage in OA is still unclear, animal studies and contemporary systematic reviews on OA in knee and hip patients show concomitant nerve injury, with a 23% prevalence rate of neuropathic pain in these patients.[9,10]

Acetaminophen, commonly known as paracetamol, was originally used as the first line of pharmacological treatment in the management of pain in knee OA. The mechanisms of acetaminophen are a combination of cyclooxygenase (COX) inhibitors, the stimulation of descending serotonergic neuronal pathways, and anti-nociceptive effects.[11] A Cochrane systematic review later demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs) are superior to acetaminophen in reducing pain and improving overall physical function.[12] Two meta-analyses also support the superior efficacy of NSAIDs in comparison to acetaminophen.[13,14] Another meta-analysis only found a small, but clinically insignificant effect, from the short-term application of acetaminophen on pain and disability in OA patients.[15] Nevertheless, due to the historical safety profile of acetaminophen, the consensus group suggests that acetaminophen can still be used as a conservative treatment in the reduction of OA pain.

Currently, growing awareness has been raised regarding complications on the long-term use of opioids. Moreover, prolonged opioid consumption may be lead to the development of opioid-induced hyperalgesia.[11] Therefore, chronic long-term

opioid usage is strongly prohibited. Current evidence suggests that opioids are not more effective than NSAIDs in terms of pain reduction or functional improvement, with the risks and side-effects of opioids clearly outweighing the benefits.[16,17] Tramadol, a weak opioid and serotonin-norepinephrine reuptake inhibitor, is promising in the treatment of knee OA, with a lower risk of complications and the potential for drug abuse. The latest Cochrane review showed that taking tramadol, or a combination of tramadol and paracetamol, for up to three months may decrease pain intensity and improve function; however, but these effects were small.[18] When opioids may be necessary, the consensus group recommends weak opioids (e.g., tramadol, codeine) as an alternative pharmacological treatment for knee OA and recommends against the chronic prolonged use of these drugs.

NSAIDs are commonly used as the main pharmacological treatment of knee OA. They have inhibitory effects on the COX enzymes, resulting in analgesic effects. Several meta-analyses proposed a small effect of NSAIDs on pain reduction in knee OA and revealed them to be superior to acetaminophen.[13,14,19] However, which NSAID provides the most optimum treatment for knee OA is still debated. A meta-analysis by Bannuru et al.[1] found that ibuprofen/diclofenac and intra-articular corticosteroid injections/hyaluronic acid had comparative efficacies in pain reduction. However, a meta-analysis by de Costa et al.[14] found that diclofenac 150 mg/day and etoricoxib 60 mg/day were one of the best medications in treating knee and hip OA.[14] A recent meta-analysis published in 2018 showed that naproxen was the most effective agent in the non-surgical treatment of knee OA.[20] The consensus group recommends the use of oral NSAIDs on

an as-needed basis when treating patients who suffer from knee OA. However, when using NSAIDs, they should still be prescribed for a minimum amount of time and at the lowest effective dose to avoid any adverse long-term effects.

Currently, there are conflicting results between studies on the effectiveness of glucosamine sulphate in treating knee OA. A multicenter, double-blind, placebo-controlled Glucosamine/Chondroitin Intervention Trial (GAIT) could not detect any significant reductions in pain reduction from glucosamine sulphate and chondroitin sulphate alone, or in combination, in patients with knee OA.[21] Contrarily, other meta-analyses showed a small effect through structural modification after the long-term use of up to two to three years with dosages of 1,500 mg/day glucosamine sulphate and 800 mg/day chondroitin.[22,23] However, the Cochrane systematic review of all randomized controlled trials did not find a superior efficacy of glucosamine sulphate over a placebo in terms of pain, stiffness, and functional outcomes .[24] Still, the review concluded that glucosamine sulphate was as safe as a placebo. Nevertheless, the efficacy of this supplement remains controversial, although its safety profile is approved. Thus, the consensus group strongly recommends the use of glucosamine sulphate in treating patients with knee OA.

Diacerein is an anthraquinone that interferes with the inflammatory cytokine, interleukin-1 (IL-1). Besides its anti-inflammatory activities, it has been proposed that diacerein may have a protective effect against subchondral bone remodeling, as well as anti-catabolic and pro-algesic properties on the synovial membrane and cartilage.[25] An updated Cochrane review confirmed that diacerein provides minimal symptomatic improvements in pain reduction, while the protective effect, defined as a slow-down of joint space narrowing, is still question

able based on their clinical relevance.[26] In July 2014, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) confirmed the safety profile of diacerein and proposed a positive risk-benefit balance in the treatment of hip and knee OA. The European Society for Clinical and Economical Aspects of Osteoporosis and Osteoarthritis (ESCEO) concluded that the risk-benefit of diacerein remains positive in the symptomatic treatment of knee OA and also proposes diacerein as a the first-line drug in the background treatment of OA in their clinical practice guideline.[27] Because the benefits outweigh the risks, the consensus group approves the use of diacerein as a medical treatment of knee OA.

Pregabalin is a calcium channel blocker that specifically binds to subunit alpha-2/delta-1 to generate antiepileptic and analgesic effects.[28] It was approved in the USA for the treatment of fibromyalgia and neuropathic pain. As previously mentioned, 23% of patients with hip or knee OA suffer from neuropathic pain[9]; this neuropathic pain is typically unresponsive to common analgesic drugs. However, only a few studies have directly investigated the efficacy of pregabalin in treating knee OA. One randomized controlled trial (RCT) compared the efficacy of meloxicam and pregabalin in knee OA.[29] While they reported that neither participants in the meloxicam or pregabalin-only group experienced a significant reduction in pain relief, or improvements in function, the combination of these two medications significantly decreased pain and improved function. Pregabalin 450 mg/day showed a significant reduction in pain intensity in fibromyalgia patients with OA comorbidity, as reported from an analysis of pooled data from 3 RCT studies.[30] From this point of view, the consensus group supports the use of pregabalin as an additional treatment for

patients with knee OA who also suffer from fibromyalgia or neuropathic pain.

Despite the lack of supporting evidence in the use of anti-spasticity and anti-spasmodic medications and muscle relaxants in treating knee OA, they are still commonly used in general practice. It is still unclear whether the combination of muscle relaxants with other analgesics can improve their efficacy. To the best of our knowledge, there are only a few RCT studies that directly assess the synergistic effects of muscle relaxants with NSAIDs in treating knee OA. One RCT reported the synergistic effect of muscle relaxants and NSAIDs in pain reduction and morphine-sparing in patients who underwent total knee arthroplasty.[31] Two other RCT studies found no significant adjuvant value when this combination of medications were used in patients with knee OA.[32,33] Nonetheless, the consensus group suggests the use of muscle relaxants, either alone or in combination with other analgesics, as an adjuvant therapy for treating knee OA.

Finally, duloxetine is a serotonin-norepinephrine reuptake inhibitor that was approved by the US Food and Drug Administration (FDA) for treating osteoarthritic pain.[11] A recent systematic review and meta-analysis revealed the superior effects of duloxetine over a placebo in both pain control and functional improvement in patients with knee OA.[34,35] When compared to NSAIDs and opioids, duloxetine showed comparable results in the Western Ontario and McMaster Universities Index (WOMAC).[36] In 2018, a randomized, double blind, placebo-controlled study confirmed the acceptable safety profile of this drug.[37] The consensus group recommends the use of duloxetine in treating patients with chronic OA pain.

คำถามที่ 2: ยากลุ่มใดเหมาะสมสำหรับการรักษาเบื้องต้นในผู้ป่วยข้อเข่าเสื่อม

Question 2: Which medication is appropriate for the initial treatment of knee OA?

ความเห็นร่วม:

- Acetaminophen
- Weak opioids
- NSAIDS; COX-1 inhibitor and COX-2 inhibitor
- Glucosamine sulphate
- Diacerein

Consensus:

- Acetaminophen
- Weak opioids
- NSAIDS; COX-1 inhibitor and COX-2 inhibitor
- Glucosamine sulphate
- Diacerein

Delegate vote: Agree 86.96%, Disagree 10.14%, Abstain 2.9% (Strong Consensus)

Justification: According to the latest evidence, combined with recommendations from the European League Against Rheumatism,[38] the American Academy of Orthopedic Surgeons[38,27], the American College of Rheumatology,[39] the Osteoarthritis Research Society International,[40] and the National Institute for Health and Care Excellence, the consensus group suggests acetaminophen[38,39], oral NSAIDs[38,39,41] glucosamine sulphate[38], diacerein[38], and a weak opioid (tramadol)[38] in the initial treatment of knee OA.

คำถามที่ 3: ยากลุ่มใดเหมาะสมสำหรับเสริมในการรักษาผู้ป่วยข้อเข่าเสื่อม?

Question 3: Which adjuvant therapies are appropriate in the conservative treatment of knee OA?

ความเห็นร่วม:

- Pregabalin
- Muscle relaxants
- Serotonin and norepinephrine reuptake inhibitors (SNRI): duloxetine

Consensus:

- Pregabalin
- Muscle relaxants
- Serotonin and norepinephrine reuptake inhibitors (SNRI): duloxetine

Delegate vote: Agree 92.65%, Disagree 5.88%, Abstain 1.47% (Strong Consensus)

Justification: Despite a paucity of high-quality studies on knee OA, due to their less serious side effects, the consensus group suggests the use of pregabalin and muscle relaxants as an adjuvant therapy in the conservative treatment of knee OA. According to recently published studies, previously mentioned, our consensus group also encourages the use of duloxetine as an additional treatment in knee OA.

คำถามที่ 4: ยากลุ่มใดเหมาะสมในการใช้รักษาแบบอนุรักษ์นิยมเป็นเวลานานในผู้ป่วยข้อเข่าเสื่อม?

Question 4: Which medication can be used in the long-term conservative treatment of knee OA?

ความเห็นร่วม:

- Glucosamine sulphate
- Diacerein

Consensus:

- Glucosamine sulphate
- Diacerein

Delegate vote: Agree 94.2%, Disagree 5.8%, Abstain 0% (Strong Consensus)

Justification: Glucosamine sulphate and diacerein are two popular supplements used currently to improve and support multiple joint conditions. Researchers suggest that the oral ingestion of these ingredients, either alone or in combination, reduces joint pain and/or improves mobility in patients with OA. There is growing awareness surrounding the medical use of these supplements to improve pain, functional outcome, and in the progression of osteoarthritis.

In 2007, Hathcock et al.[42] reported the observed safe level (OSL) and highest observed intake (HOI) to assess the risk of supplementing with glucosamine sulphate and chondroitin. The study reports a complete absence of adverse effects at even the highest levels of intake tested in human clinical trials, i.e., 2,000 mg/d for glucosamine sulphate and 1,200 mg/d for chondroitin sulphate.

Diacerein has several adverse effects, including common gastrointestinal disorders (soft stools and diarrhea), common mild skin reactions, and, in rare instances, hepatobiliary disorders. Although the laxative property of diacerein is dose-dependent, it is recommended to start the medication at half the recommend dose (50mg/day) to minimize these effects.[43] Several studies

have shown that paracetamol and NSAIDs may potentially cause severe hepatic, gastrointestinal, renal, cutaneous, and cardiovascular reactions.[44,45,46,47,48] The ESCEO concluded that the risk-benefit balance was positive for diacerein in the symptomatic treatment of hip and knee OA.[25]

คำถามที่ 5: ยาคลายกล้ามเนื้อสามารถใช้เป็นยารักษาเสริมในผู้ป่วยโรคข้อเข่าเสื่อมได้

Question 5: Can muscle relaxants be used as an appropriate adjuvant treatment in knee OA?

ความเห็นร่วม: ยาคลายกล้ามเนื้อสามารถใช้รักษาอาการปวดจากกล้ามเนื้อในผู้ป่วยโรคข้อเข่าเสื่อมได้

Consensus: Muscle relaxants can be used to treat muscle pain in knee OA.

Delegate vote: Agree 92.75%, Disagree 4.35%, Abstain 2.9% (Strong Consensus)

Justification: Patients with knee OA also experience significant muscle impairment, which affects their physical function and can cause muscle pain and spasms.[49] Therefore, treating musculoskeletal symptoms may help to decrease pain in these patients. Among several types of medications, muscle relaxants are widely used as an adjunctive medication in the treatment of musculoskeletal pain.

Although there is no evidence on its efficacy in patients with knee OA, systematic reviews and meta-analyses have supported the use of muscle relaxants in the short-term relief of acute low back pain.[50] Some evidence also suggests that orphenadrine is effective when compared to placebos

in patients with musculoskeletal problems.[31] Moreover, post-operative patients who underwent TKA and were treated with a combination of a muscle relaxants with celecoxib for 2 weeks, showed a significant decrease in their postoperative Visual Analog Scale (VAS) pain scores on ambulation and morphine consumption, with improved postoperative range of motion (ROM).[51] Therefore, muscle relaxants can be used as an adjuvant medication in patients with knee OA and musculoskeletal symptoms. The general practitioner should consider which medical agent to prescribe based on the drug's side-effects and abuse potential, the patient's preferences, and possible drug interactions.[50]

คำถามที่ 6: ยาพรีกาบาลินสามารถใช้เป็นยารักษาเสริมในผู้ป่วยโรคข้อเข่าเสื่อมได้

Question 6: Can pregabalin be used as an appropriate adjuvant treatment in patients with knee OA?

ความเห็นร่วม: ยาพรีกาบลินสามารถใช้รักษาอาการปวดจากกล้ามเนื้อในผู้ป่วยโรคข้อเข่าเสื่อมได้

Consensus: Pregabalin can be used to treat myofascial pain in knee OA.

Delegate vote: Agree 84.06%, Disagree 7.25%, Abstain 8.7% (Strong Consensus)

Justification: Pain from knee OA is usually classified as nociceptive pain; however, a neuropathic component is possible, especially in patients with severe pain and disability. A study showed that 26% of knee OA pain was neuropathic pain. Treating neuropathic pain in knee OA may help to decrease the

severity of pain and level of disability in patients. Pregabalin is an effective therapeutic agent for neuropathic pain with a high safety profile.[52]

Although there is currently a lack of strong evidence on the efficacy of using pregabalin in the treatment of knee OA, a randomized prospective study did show that combining pregabalin with meloxicam reduced the amount of pain in patients with knee OA.[29] Moreover, combining pregabalin with celecoxib can be effective in decreasing acute pain after TKA with no significant side effects.[53] Therefore, a general practitioner should consider pregabalin as an adjuvant medication in treating patients with knee OA who experience characteristics of neuropathic pain.

คำถามที่ 7: ยา duloxetine สามารถใช้เสริมในการรักษาผู้ป่วยข้อเข่าเสื่อมหรือไม่?

Question 7: Can duloxetine be used as an appropriate adjuvant treatment in knee OA?

ความเห็นร่วม: ยา duloxetine สามารถใช้เสริมในการรักษาผู้ป่วยข้อเข่าเสื่อมสำหรับการรักษาอาการปวดเรื้อรังได้

Consensus: Duloxetine can be used to treat chronic pain in knee OA.

Delegate vote: Agree 76.81%, Disagree 4.35%, Abstain 18.84% (Strong Consensus)

Justification: SNRIs not only have the benefit of reducing depressive symptoms but they also reduce symptoms related to central and peripheral neuropathic pain. Duloxetine, a SNRI, has been studied for use in the treatment of patients with

widespread degenerative diseases. A review of duloxetine showed that it reduces pain and fatigue while improving physical and mental performance in comparison to a placebo.[54]As of June 2008, the FDA has approved this drug in the treatment of fibromyalgia. In the US, duloxetine is used in managing pain disorders, including diabetic peripheral neuropathic pain (DPNP), fibromyalgia, and chronic musculoskeletal pain, including discomfort due to OA and chronic low back pain . A recent systematic literature review followed by a meta-analysis was performed to assess the efficacy of duloxetine versus other commonly used first-line OA treatments, including NSAIDs and opioids. The study incorporated a more inclusive set of OA symptoms by using the WOMAC, which includes subscales for function and stiffness, as well as for pain. Therefore, it provides a broader measure of OA health than measurement systems that focus solely on pain. This meta-analysis found no differences between duloxetine and other first-line oral treatments for OA based on the total WOMAC scores after approximately 12 weeks of treatment. However, after adjusting for baseline pain scores, duloxetine showed higher efficacy than both tramadol and hydromorphone, but not for other treatments, including etoricoxib.[36] Some early evidence suggests that a combination of analgesics with different mechanisms of action may be more effective than a single analgesic; however, combination therapy may increase the risk of adverse events.[55-57] Based on this evidence, duloxetine may be useful as an adjunctive drug in treating chronic pain from OA. However, due to the advanced age of most patients with OA, along with a higher prevalence of comorbid conditions, such as renal and hepatic impairment, substantial alcohol intake and uncontrolled hypertension, this drug should be prescribed with caution.

คำถามที่ 8: สามารถใช้ยากลุ่ม Symptomatic Slow Acting Drugs for Osteoarthritis (SYSADOA) ร่วมกันสองตัวในการรักษาผู้ป่วยข้อเข่าเสื่อมได้หรือไม่?

Question 8: Can a combination of two Symptomatic Slow Acting Drugs for Osteoarthritis (SYSADOA) be used in the treatment of knee OA?

ความเห็นร่วม: สามารถใช้ยากลุ่ม SYSADOA ร่วมกันสองตัวในการรักษาผู้ป่วยข้อเข่าเสื่อมได้ในกรณีที่ยาสองตัวมีกลไกการออกฤทธิ์แตกต่างกัน

Consensus: A combination of SYSADOA can be used to treat knee OA when each drug has a different mechanism of action.

Delegate vote: Agree 73.91%, Disagree 13.04%, Abstain 13.04% (Strong Consensus)

Justification: OA of the knee is a common joint disorder in elderly patients, with a multi-faceted etiology. The initial treatment of knee OA should be non-operative. The aims of SYSADOAs are to preserve joint structure and function, as well as to provide certain disease-modifying effects. Commonly used medications include hyaluronic acid (HA), chondroitin sulphate (CS), glucosamine sulphate (GlcN)[58], and diacerein.

The mechanisms of these medications differ from one another in terms of body distribution. For example, due to the large molecular weight of HA, this medication is poorly absorbed by the gastrointestinal tract, and is therefore administered locally via injection into the joint. With its high molecular weight, HA can reverse inflammatory effects by inactivating cell-surface proteins, TLR4, CD44, and ICAM1, and by disrupting the binding of extra cellular matrix fragments

or lipopolysaccharide[59,60], as well as by increasing the expression of IRAK-M and MKP-1.[61,62]

As for CS, several mechanisms work together to decrease the inflammatory processes in knee OA. One study found a significant increases in HA concentrations and intrinsic viscosity of synovial fluid in humans with knee OA who were treated for ten days with 800 mg/day of CS.[63] The mechanisms that lead to CS-induced synthesis of HA are the up-regulation of HAS1 and HAS2.[64,65] This effect may be explained by the engagement of CS to β1-integrin[66], and by the up-regulation of transforming growth factor-β1 (TGF-β1)[67,68] and HAS2.[69,70] For this reason, inhibition of NF-KB activation via CS is possible due to an increase in high molecular weight HA (HMW-HA) synthesis. CS has also been shown to decreases synovitis[21] and subchondral lesions.[71] *In vitro*, CS reduces IL-1β-induced inflammatory reactions in the subchondral bone[72,73] and in the synovial membranes.[74]

According to Ohara et al.[75], chondrocytes express GLUT1, -2, -3, -4, and -5, which are responsible for glucosamine sulphate uptake in human knees. Several mechanisms contribute towards a GlcN-induced decline in the NF-KB nuclear translocation. For example, GlcN reduces inflammation by decreasing NF-KB nuclear translocation and by prohibiting the transcription of proteolytic and pro-inflammatory target genes. This occurs through the process of protein O-GlcNAcylation, primarily of IKKα and IKBα.

Lastly, diacerein is classified as a symptomatic slow acting drug or SYSADOA that inhibits IL-1, which is responsible for the destruction of cartilage. Diacerein also increases the production of TGF-β collagen[58], proteoglycans, and hyaluronan. This results in the stimulation of chondrocyte proliferation,

increased synthesis of matrix components, as well as the restoration of synovial fluid properties.

According to the consensus group, due to different mechanisms of action for each SYSADOA, combining several types of these medications may have some benefits for patients with OA; however, there is currently no clear evidence to support this rationale.

คำถามที่ 9: ยาชื่อสามัญเดียวกัน สามารถใช้ทดแทนกันได้

Question 9: Are drugs with the same generic names interchangeable?

ความเห็นร่วม: ใช่

Consensus: Yes

Delegate vote: Agree 42.03%, Disagree 50.72%, Abstain 7.25% (No Consensus)

Justification: The use of generic medications greatly reduces the cost of healthcare expenditure for both the governments and patients. A generic drug is a pharmaceutical drug that has the same active chemical substance as the original, with an equivalent medical profile and performance. However, while they use the same active pharmaceutical ingredients, the production process, formulation, and excipients may be different.

According to most government regulations, a generic drug must contain the same active ingredients as the original brand name formulation. Furthermore, generic brand drugs must be identical to, or within an acceptable bioequivalent range, to the brand name in both pharmacokinetic and pharmacodynamics properties to ensure its effectiveness, strength, stability, and quality.

Although the use of generics may be interchangeable, there are still concerns regarding certain medications in terms of variances in their efficacy, such as for glucosamine sulphate. Glucosamine sulphate is a widely used supplement that helps to reduce pain in patients with osteoarthritis. Currently on the market, there are patented crystalline glucosamine sulphate (pCGS) formulations (Rottapharm Madaus), and generic, or over-the-counter, supplements. Over-the-counter glucosamine sulphate formulations in food supplements mostly contain glucosamine hydrochloride salt (GH).[76] In pharmacokinetic studies by Jackson et al. and Persiani et al., they showed that the level of mean plasma concentration was at a steady state of 9 μM for 1,500 mg pCGS and only 1.2 μM for GH (500 mg tid).[21,77] A multicenter and double-blind study by Clegg et al. of 1,583 patients with symptomatic knee OA found that the use of GH failed to show any benefits over placebos. The differences in dosing regimen and pharmaceutical formulation may play a major role in affecting the bioavailability of GH, which may help to explain the negative results with this formulation.[21] Russell et al. performed a study assessing the quality of non-prescription grade glucosamine formulations by analyzing the content of active ingredients in 14 commercial over-the-counter glucosamine sulphate formulations. The study reported that the amount of active ingredient ranged from 59% to 138% of the labeled doses.[76,78]

As for a distinction in the efficacy of crystalline glucosamine sulphate and glucosamine hydrochloride, the ESCEO encourages using prescription pCGS over other glucosamine preparations.[76]

คำถามที่ 10: ยาในกลุ่มใดที่ต้องระมัดระวังเป็นพิเศษในการนำมาใช้กับผู้ป่วยข้อเข่าเสื่อมที่มีโรคไตเรื้อรังร่วมด้วย?

Question 10: Which drugs should be used with caution in treating knee OA in patients with chronic kidney disease?

ความเห็นร่วม: ควรหลีกเลี่ยงยา NSAIDs และ acetaminophen ขนาดสูง (>3 กรัม/วัน) ในผู้ป่วยข้อเข่าเสื่อมที่มีโรคไตเรื้อรังร่วมด้วย

Consensus: NSAIDs and high dose acetaminophen (>3g/day) should be avoided in patients with chronic kidney disease.

Delegate vote: Agree 98.55%, Disagree 0%, Abstain 1.45% (Strong Consensus)

Justification: Globally, acetaminophen, or paracetamol, is one of the most commonly used analgesics and is a first-line pharmacologic agent for the symptomatic treatment of mild to moderate pain as recommended by the World Health Organization (WHO). This is due to their low-cost and fewer side effects when taken at less than 4,000 mg per day. Although acetaminophen-induced liver necrosis has been studied extensively, the extrahepatic manifestations of acetaminophen toxicity are currently not well-described in the literature, with no warnings from the FDA regarding renal toxicity or complications. However, although uncommon, renal injury, oliguria, and acute renal failure are known side-effects. The onset is usually after a hepatic injury that is already apparent. Maximal renal injury also lags beyond peak liver injury, with recovery more protracted.[79] Renal failure may also be seen in cases of FHF and hepatorenal syndrome, while isolated nephrotoxicity without hepatic injury rarely occurs.[80,81] Renal insufficiency occurs in approximately 1-2% of patients with acetaminophen

overdose. However, the current average patient with knee OA is typically older, with more comorbidities, and are exposed to more diagnostic and therapeutic procedures and with a higher potential to harm kidney function. Drugs that are nephrotoxic exert their toxic effects by one or more common pathogenic mechanisms. Drug-induced nephrotoxicity tends to be more common among certain patients and in specific clinical situations. Some patient-related risk factors for drug-induced nephrotoxicity include being older than 60 years, having underlying renal insufficiency (e.g., glomerular filtration rate of less than 60 mL per minute per 1.73 m^2), volume depletion, diabetes, heart failure, and sepsis.[82-86] There is also evidence for the loss of renal function in women following the long-term consumption of high doses of paracetamol (>3 g/day, odds ratio [OR]=2.04; 95% confidence interval [CI]: 1.28-3.24), with a decline in glomerular filtration rate (GFR) >30 mL/min, and an increase in hypertension in both men (relative risk [RR]= 1.34; 95% CI:1.00-1.79) and women (RR=2.00; 95% CI: 1.52-2.62).[87-89] General preventative measures include using alternative non-nephrotoxic drugs whenever possible; correcting risk factors, if possible; assessing baseline renal function before initiation of therapy, followed by adjusting the dosages; monitoring renal function and vital signs during therapy; and avoiding nephrotoxic drug combinations.

In patients with symptomatic hip or knee OA, NSAIDs should be used at their lowest effective dose with long-term use avoided if possible.[90]

คำถามที่ 11: ยาในกลุ่มใดที่ต้องระมัดระวังเป็นพิเศษในการนำมาใช้กับผู้ป่วยข้อเข่าเสื่อมที่มีโรคหัวใจร่วมด้วย?

Question 11: Which drugs should be used with caution for treating knee OA in patients with cardiovascular disease?

ความเห็นร่วม: ยากลุ่ม COX-2 inhibitor ควรใช้อย่างระมัดระวังเป็นพิเศษในการรักษาข้อเข่าเสื่อมในผู้ป่วยโรคหัวใจ

Consensus: COX-2 inhibitors should be used with caution in patients with cardiovascular disease.

Delegate vote: Agree 86.96%, Disagree 8.7%, Abstain 4.35% (Strong Consensus)

Justification: NSAIDs represent a highly heterogeneous group of widely prescribed agents in the management of acute pain as, well as for the symptomatic relief of chronic pain and inflammation associated with OA and rheumatoid arthritis (RA).

Based on several short-term trials, there is abundant evidence that shows that NSAIDs are associated with more adverse effects than acetaminophen. In 2004, Zhang et al.[13] showed that NSAIDs were associated with gastrointestinal (GI) discomfort more frequently than acetaminophen (RR ¼: 1.35; 95% CI: 1.05-1.75).This was also confirmed in a more recent Cochrane systematic review on short-term RCTs (RR ¼: 1.47; 95% CI: 1.08-2.00).[12] More importantly, NSAIDs can cause serious GI complications, such as peptic ulcers and perforations and bleeds (PUBS); these risks also increase with age, the concurrent use of other medications, and with the duration of therapy.[91]

NSAIDs are further classified into traditional NSAIDs and cyclooxygenase (COX)-2 inhibitors (coxibs), with the latter posing potentially fewer gastrointestinal risks. In 2005, rofecoxib was

withdrawn from the market due to concerns surrounding the risk of heart attack and stroke with its long-term use, with clinical practices beginning to focus more on the cardiovascular versus gastrointestinal safety of coxibs. Since then, many coxibs have remained unapproved by the FDA or have been removed entirely from the market. This article explains how coxibs have refocused attention on the cardiovascular safety of NSAIDs and what are the general implications of this. COX-2 activity/specificity is a factor associated with increased cardiovascular risks; however, these risks cannot be attributed to coxibs alone. The traditional NSAIDs (i.e., meloxicam, etodolac, and nabumetone) also have significant COX-2 specificity; however, naproxen and ibuprofen have less specificity.

The results from a meta-analysis[92] show that NSAIDs are a pharmacologic class associated with increased CVR when compared to no anti-inflammatory treatments (RR: 1.24; 95% CI:1.19-1.28). This association seems to be only slightly higher for coxibs (RR coxibs: 1.22; 95% CI: 1.17-1-28) compared to classical NSAIDs (RR:1.18; 95% CI: 1.12-1.24). For coxibs, our findings are consistent with those previously estimated in 2013, by the Coxib and traditional NSAIDS trialists' (CNT) Collaboration[46], which found a higher risk of major cardio vascular events (RR coxibs=1.37; 95% CI: 1.14-1.66). Subgroup analyses by dose revealed a higher CVR for coxibs when compared to classical NSAIDs.[92] The various dose effects for coxibs were noted in an earlier meta-analysis.[93] However, it should be highlighted that in a meta-analysis[92], a low dose of celecoxib, etoricoxib, ibuprofen, or naproxen did not show any statistically significant CVR.

The use of the marketed coxibs, celecoxib and etoricoxib. Are related to a statistically significant CVR increase. Etoricoxib CVR appears to be higher than in celecoxib. This increment is similar to what is seen in classical NSAIDs CVR. Evan at low doses, the risk resulting from the combined exposure to NSAIDs, both classical or coxibs, remained statistically significant. Therefore, the risk-benefit balance should be assessed for each individual patient when prescribing NSAIDs. Only a low dose of celecoxib, etoricoxib, ibuprofen, or naproxen should be prescribed when NSAID use is necessary.

คำถามที่ 12: ยาในกลุ่มใดที่ต้องระมัดระวังเป็นพิเศษในการนำมาใช้กับผู้ป่วยข้อเข่าเสื่อมที่มีโรคตับเรื้อรังร่วมด้วย?

Question 12: Which drug should be used with caution for treating knee OA in patients with chronic liver disease?

ความเห็นร่วม: ควรใช้ยา NSAID และ acetaminophen อย่างระมัดระวังเป็นพิเศษในผู้ป่วยข้อเข่าเสื่อมที่มีโรคตับเรื้อรังร่วมด้วย

Consensus: NSAIDs and acetaminophen should be used with caution in patients with chronic liver disease.

Delegate vote: Agree 95.65%, Disagree 1.45%, Abstain 2.9% (Strong Consensus)

Justification: Acetaminophen, or paracetamol, is a widely used nonprescription analgesic and antipyretic medication for mild-to-moderate pain and fever and is widely used in patients with knee OA. Although harmless at low doses, acetaminophen has direct hepatotoxic potential when taken at overdose levels and can cause acute liver injury and death from acute liver failure. Acetaminophen can even cause transient serum

aminotransferase elevations at therapeutic doses. The FDA recommends the oral dose to not exceed the acetaminophen maximum total daily dose (4 grams/day). Chronic therapy with acetaminophen at doses of 4 grams daily has been found to lead to transient elevations in serum aminotransferase levels in a proportion of subjects, generally starting after 3 to 7 days, with peak values rising above 3-fold in 39% of patients.[94] Acetaminophen hepatotoxicity most commonly arises after a suicide attempt using more than 7.5 grams (generally more than 15 grams) as a single overdose. Similar injury can occur with high therapeutic or supratherapeutic doses of acetaminophen given over several days for the treatment of pain and not as a purposeful suicidal overdose. Although toxic ingestion causing hepatic failure is usually in excess of 150 mg/kg, an increasing number of reports suggest that lower doses of acetaminophen-induced hepatotoxicity may confer acute liver injury and liver failure.[95-98] However, recent concerns over the safety profile of paracetamol raise questions over its routine and chronic use. There is mounting evidence on an increased risk of upper GI events with paracetamol use, as well as an elevated risk of severe liver injury with a high daily dose. Treatment with high-doses of paracetamol (>3 g/day) is associated with a greater risk of hospitalization due to GI perforation, ulceration, or bleeding (PUB), than with lower daily doses of paracetamol (hazard ratio [HR]=1.20; 95%CI: 1.03-1.40).[99] In primary care, paracetamol may still be used to treat pain in mild-moderate OA at daily doses up to 3g/day.

คำถามที่ 13: เราควรใช้ glucosamine sulphate รักษาโรคข้อเข้าเสื่อมเป็นระยะๆ หรือไม่?

Question 13: Should glucosamine sulphate be used intermittently?

ความเห็นร่วม: ไม่ใช่ มีการแนะนำให้ใช้ glucosamine sulphate อย่างต่อเนื่อง เพื่อให้ได้รับผลการป้องกันข้อเข่าเสื่อมจากยา กลุ่ม disease-modifying osteoarthritis drugs (DMOADs) อีกทั้งยังไม่พบผลข้างเคียงจากยากลุ่มนี้ ดังนั้นการใช้ยาเป็นระยะๆ จึงไม่มีความจำเป็น

Consensus: No, due to the prevention effects needed in disease-modifying treatments for osteoarthritis (DMOAD), long-term use is suggested for glucosamine sulphate. And due to the lack of severe or serious side-effects, intermittent use of this drug is not effective.

Delegate vote: Agree 85.51%, Disagree 7.25%, Abstain 7.25% (Strong Consensus)

Justification: Bruyere et al.[100] performed a long-term follow-up study on the use of glucosamine sulphate and concluded that treating knee OA with glucosamine sulphate for at least 12 months and up to 3 years may delay the necessity of undergoing a total knee replacement, after an average follow-up period of 5 years after drug discontinuation.

Additionally, the Pharmaco-Epidemiology of GonArthroSis (PEGASus) study, conducted by the French Health Authorities in collaboration with a panel of French rheumatologists and epidemiologists, found that only glucosamine sulphate achieved a significant reduction in NSAIDs usage.

Prescribing glucosamine sulphate is considered safe and effective, with no significant adverse events. In addition to reducing the use of NSAIDs, which have been shown to

cause potentially severe hepatic, gastrointestinal, renal, and cardiovascular reactions, continuing the medication may not be necessary.

คำถามที่ 14: การใช้พาราเซตตามอลเป็นยาบรรเทาปวดในผู้ป่วยโรคข้อเข่าเสื่อม ยังคงมีความเหมาะสมหรือไม่?

Question 14: Is acetaminophen still appropriate in the conservative treatment of knee OA?

ความเห็นร่วม: แม้ว่าพาราเซตตามอลจะมีประสิทธิภาพในการบรรเทาปวดในผู้ป่วยโรคข้อเข่าเสื่อมได้ไม่เท่ากับยาในกลุ่ม NSAID แต่ก็ยังคงเป็นยาบรรเทาปวดที่มีความเหมาะสมในการใช้ ถ้าใช้อย่างเหมาะสมและระมัดระวัง โดยเฉพาะการใช้ในขนาดที่สูงและเป็นระยะเวลานาน

Consensus: Acetaminophen is still suitable for patients with knee OA, although it is less effective in the symptomatic control compared to the NSAIDs groups. Overall, acetaminophen should be used with care and caution regarding high dosages and long-term use.

Delegate vote: Agree 94.2%, Disagree 5.8%, Abstain 0% (Strong Consensus)

Justification: Acetaminophen, or paracetamol, is often recommended as the first-line drug to treat knee pain in various medical practices, especially in mild to moderate pain, as they are cost-effective and have fewer side effects when prescribed at less than 4,000 mg per day. In 2003, the EULAR provided recommendations from an evidence-based approach on the management of knee OA.[38] In 2012, the ACR made recommendations on the use of nonpharmacologic and

pharmacologic therapies for OA of the hand, hip, and knee[101] and the OARSI created guidelines for the non-surgical management of knee OA.[40] In 2006, a Cochrane review[12] concluded, in placebocontrolled RCTs, that acetaminophen was superior to a placebo in five of the seven RCTs, with similar safety profiles. Overall, the evidence to date suggests that NSAIDs are superior to acetaminophen in improving knee and hip pain in people with OA. In the randomized controlled RCTs, acetaminophen was found to be less effective overall than NSAIDs in terms of pain reduction and global assessments, as well as for improvements in functional status. No significant differences were found between the safety of acetaminophen and NSAIDs, although patients taking traditional NSAIDs were more likely to experience an adverse GI event (RR=1.47; 95% CI: 1.08-2.00). However, the median trial duration was only 6 weeks; therefore, it is difficult to assess adverse outcomes during a relatively short time period. In patients with OA experiencing moderate-to-severe levels of pain, NSAIDs appear to be more effective than acetaminophen. However, recent concerns over the safety profile of acetaminophen have raised questions over its routine and chronic use. Treatment with high-doses of acetaminophen (>3 g/day) are associated with a greater risk of hospitalization due to GI perforation, ulceration, or bleeding (PUB), than lower daily doses (HR=1.20; 95%CI: 1.03-1.40).[99]There is also evidence showing the loss of renal function in women following the long-term consumption of high doses of acetaminophen (>3 g/day)(OR=2.04; 95% CI: 1.28-3.24), with a decline in glomerular filtration rate (GFR) >30 mL/min, and an increase in hypertension in both men (RR=1.34; 95% CI: 1.00-1.79] and women (RR=2.00; 95% CI: 1.52-2.62) (6-8). However, if acetaminophen is ineffective, or insufficiently

effective, the physician should consider stopping and/or switching treatments, or combining it with other therapies.

คำถามที่ 15: ในการใช้ยา glucosamine sulphate เพื่อรักษาโรคข้อเข่าเสื่อม จำเป็นต้องมีการจำแนกของอายุผู้ป่วยหรือไม่?

Question 15: Is there an age criterion in the use of glucosamine sulphate in patients with knee OA?

ความเห็นร่วม: Glucosamine sulphate สามารถใช้ได้ในคนไข้ทุกกลุ่มอายุที่มีผล X-ray Kellgren and Lawrence classification ตั้งแต่ grade I ขึ้นไป

Consensus: Glucosamine sulphate can be used in patients with knee OA where radiographs show a Kellgren and Lawrence classification Grade over I in all patient age-groups.

Delegate vote: Agree 92.65%, Disagree 2.94%, Abstain 4.41% (Strong Consensus)

Justification: Osteoarthritis is common in people over 50 years old, with glucosamine sulphate found to be effective in controlling OA. The medication itself has shown to have structure-modifying effects and to delay the time until surgery is needed.[102] In 2007, Hathcock et al.[102], reported the complete absence of adverse effect, even at the highest levels of intake in human clinical trials (i.e., 2,000 mg/day for glucosamine sulphate and 1,200 mg/day for chondroitin sulphate)

In a meta-analysis by Xiaoyue Zhu et al.[103], the mean average ages from several studies were between 55 to 65 years. However, in a study by Persiani et al. on twelve healthy volunteers, the mean age was 31.5 $\pm$ 6.4 years. However, the purpose of this study was to investigate oral pharmacokinetic and dose-

proportionality of glucosamine sulphate after administration.[102] Currently, there is no specific age recommendation for glucosamine sulphate treatment. Additionally, there have been a lack of studies regarding children, with the long-term effects on the bones and joints of growing children unknown.

As for expert opinion, due to the safety profile of glucosamine sulphate and its ability to alter the progression of osteoarthritis, young active patients could benefit from its advantages. Therefore, we recommend the use of glucosamine sulphate as a treatment based on the osteoarthritis stage of the patient.

คำถามที่ 16: ในการใช้ยา diacerein เพื่อรักษาโรคข้อเข่าเสื่อม จำเป็นต้องมีการจำแนกของอายุผู้ป่วยหรือไม่?

Question 16: Is there an age criterion for the use of diacerein in patients with knee OA?

ความเห็นร่วม: Diacerein สามารถใช้ได้ในคนไข้ทุกกลุ่มอายุที่มีผล X-ray Kellgren and Lawrence classification ตั้งแต่ grade I ขึ้นไป

Consensus: Diacerein can be used in symptomatic patients with knee OA where radiographs show a Kellgren and Lawrence classification Grade I and greater in all patient age-groups.

Delegate vote: Agree 92.75%, Disagree 2.9%, Abstain 4.35% (Strong Consensus)

Justification: Osteoarthritis (OA) of the knee is a disease affecting synovial joints and is characterized by degradation and loss of articular cartilage with subchondral bone remodeling, osteophyte formation, and synovial membrane inflammation. Major symptom are pain and disability.[104,105]

Objectives of OA management are to reduce symptoms, minimize functional disability, and limit the progression of structural changes, with the ultimate goal of delaying or avoiding arthroplasty.

Diacerein, an anthraquinone derivative, is a symptomatic slow-acting OA drug. Defined as having a slow onset of efficacy, usually after 2-4 weeks of treatment, and a carryover effect once treatment is stopped.[106]

Mechanism of action of diacerein is IL-1β inhibition that can prevent cartilage damage and inhibit pain pathway. In vitro studies have shown that diacerein not only inhibits IL-1β[107-109], but also stimulates the production of cartilage growth factors such as transforming growth factor-β[110] that can stimulate cartilage growth.

There are many RCT it has been shown to significantly reduce pain in osteoarthritis patients[43,111,112], and proven the efficacy and safety of diacerein in osteoarthritis knee treatment when comparing with placebo[43,113] or piroxicam with less gastrointestinal side effect.[114]

The major side effect of diacerein is non-fetal diarrhea. The study in Thai patients show this side effect can lower by reduce dose by half for the first month. 3-year RCT study comparing diacerein and placebo used in term of cartilage loss prevention shown that patients in diacerein group had significant less cartilage loss than the placebo group. That is structure-modifying effects of Diacerein.[113]

As for our expert's opinion, due to the safety profile of diacerein and its ability to alter the progression of osteoarthritis, young patients could benefit from the follow advantages. We recommend the use of diacerein for treatment according to all osteoarthritis stage and age group.

คำถามที่ 17: ยาในกลุ่ม weak opioids (ตัวอย่าง เช่น tramadol, codeine) มีประสิทธิภาพ สำหรับใช้ในการรักษาข้อเข่าเสื่อม แบบประคับประคอง

Question 17: Are weak opioids (e.g., tramadol, codeine) effective in the conservative treatment of knee OA?

ความเห็นร่วม: Weak opioid มีประสิทธิภาพในการรักษาผู้ป่วยข้อเข่าเสื่อม โดยสังเกตได้จากการลดลงของคะแนนความปวด

Consensus: Weak opioids are effective in treating patients with knee OA, with decreases observed in pain scores.

Delegate vote: Agree 98.55%, Disagree 1.45%, Abstain 0% (Strong Consensus)

Justification: Opioids are substances often used in the relief of both acute and chronic pain. Opioid drugs produce their actions at a cellular level by activating opioid receptors in both the central and peripheral nervous systems. Weak opioids (e.g., codeine and tramadol) are central analgesics with a low affinity for opioid receptors. They are useful in mild-to-moderate pain, with minimal sedative effects or abuse potential, but with analgesic effects that are weaker than morphine.[115] The maximal dose of codeine is 360 mg/day, with tramadol at 400 mg/day. The efficacy of codeine and tramadol is improved when combined with paracetamol.[116] Long-term opioid use may have fewer life-threatening risks (gastrointestinal and renal complications, especially in elderly patients) than the long-term daily uses of NSAIDs.[117,118] However, common side-effects include sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression.[119]

A Cochrane meta-analysis systematic review found that patients with OA who received tramadol or tramadol/paracetamol experienced less pain, experienced improvements in joint stiffness and function, and had an increase in overall well-being. However, patients who received tramadol may experience side-effects that may cause patients to stop taking the drug.[118] Short-term studies (4-12 weeks) on patients with chronic OA pain found that the efficacy of opioids were superior to placebos; however, the tolerability of opioids were inferior to placebos. Opioids and placebos did not differ in terms of safety. Short-term pain treatment using opioids in patients with chronic OA may be considered in certain patients given the evidence that weak opioids may works when properly prescribed.[120]

คำถามที่ 18: ยากลุ่ม NSAIDs ควรใช้เป็นยาหลักกลุ่มแรกในการรักษาผู้ป่วยข้อเข่าเสื่อม?

Question 18: Should NSAIDs be prescribed as the first-line drug for knee OA?

ความเห็นร่วม: ใช่

Consensus: Yes

Delegate vote: Agree 91.3%, Disagree 7.25%, Abstain 1.45% (Strong Consensus)

Justification: OA is the most common form of joint disease and the leading cause of pain in the elderly.[121] Pain symptoms associated with OA are caused by many factors, including mechanical symptoms that result in bone-on-bone OA and inflammation around the knee joint. Management of OA pain is based on a multidisciplinary approach, with NSAIDs as the

current main form of treatment.[122,123] In the US, about 65% of patients with OA are prescribed NSAIDs, making them one of the most widely used drugs in this patient population.[124]

There is strong evidence supporting the clinical effectiveness of NSAIDs, with prescribed use corresponding to decreased pain and improvements in function and quality of life.

In 2013 in the US, based on the AAOS's evidence-based guidelines on the treatment of knee OA[125], NSAIDs were highly recommended for patients with symptomatic knee OA, in both an oral and topical form. This recommendation included studies on both selective COX-2 inhibitors and non-selective NSAIDs.

According to a consensus statement by the ESCEO[126] in 2015, it was recommended that oral NSAIDs maintain a central role in the advanced management of persistent symptoms. However, oral NSAIDs are highly heterogeneous in terms of their gastrointestinal and cardiovascular safety profile, with patient stratification and careful treatment selection advocated to minimize the risks. Topical NSAIDs may provide an additional symptomatic treatment with the same degree of efficacy as oral NSAIDs and without the systemic safety concerns.

In 2014, the OARSI guidelines on the non-surgical management of knee OA[40] recommended that oral non-selective NSAIDs and selective COX-2 inhibitors could be used in patients with knee OA without co-morbidities, such as cardiovascular diseases or chronic renal failure.

คำถามที่ 19: ยากลุ่ม NSAIDs มีประสิทธิภาพในการรักษาผู้ป่วยข้อเข่าแบบอนุรักษ์นิยม?

Question 19: Are NSAIDs effective in the conservative treatment of patients with knee OA?

ความเห็นร่วม: ยากลุ่ม NSAIDs มีประสิทธิภาพในการรักษาผู้ป่วยข้อเข่าเสื่อม

Consensus: NSAIDs are effective in treating patients with knee OA.

Delegate vote: Agree 100%, Disagree 0%, Abstain 0% (Unanimous Consensus)

Justification: Knee OA is a significant health problem with an estimated 45% lifetime risk of development. Therefore, effective nonsurgical treatments are needed to manage symptoms. NSAIDs are the current backbone of OA pain management.

Bjordal et al.[127] reported a meta-analysis on randomized placebo-control trails regarding oral NSAIDs therapy in patients with moderate to severe pain. They found maximum efficacies compared to placebos at 1-3 weeks and that topical NSAIDs offer limited pain relief over a placebo within 1-2 weeks.

Da Costa et al.[14] reported a network meta-analysis showing that diclofenac 150 mg/day seemed to be the most effective in terms of managing pain and physical disability in OA and were superior to the maximum doses of frequently used NSAIDs, including ibuprofen, naproxen and celecoxib. Etoricoxib, at a maximum dose of 60 mg/day, is as effective as diclofenac 150 mg/day for the treatment of pain, but its effects on physical disability are imprecise. Although our findings suggest that some NSAIDs have a clinically relevant treatment

effect on OA pain, their benefit has to be weighed against their potential harmful effects.[128] For example, previous analyses suggest that diclofenac increases the risk for cardiovascular events, especially cardiovascular death, but have similar upper gastrointestinal complications to COX-2 inhibitors.[129,46] By contrast, naproxen does not seem to increase cardiovascular risk, but does substantially increase the likelihood of upper gastrointestinal complications. Appropriate drug selection is a major challenge in patients with OA who are often elderly and are polypharmacy.

Jevsevar et al.[20] reported a network meta-analysis to determine the clinical efficacy relevance of NSAIDs, acetaminophen, intra-articular (IA) corticosteroids, IA platelet-rich plasma (PRP), and IA hyaluronic acid (HA) by comparing them with each other, as well as with oral and IA placebos. For pain, all active treatments performed better than oral placebos. For function, naproxen was the only treatment that showed any clinical significance compared with an oral placebo.

คำถามที่ 20: สามารถใช้ยากลุ่ม NSAIDs ร่วมกับยากลุ่ม SYSADOA ในการรักษาผู้ป่วยข้อเข่าเสื่อมได้

Question 20: Can the combination of NSAIDs and SYSADOAs be used in treating patients with knee OA?

ความเห็นร่วม: สามารถใช้ยากลุ่ม NSAIDs เพื่อช่วยลดการอักเสบของข้อเข่าได้เป็นเวลา 2 สัปดาห์และสามารถใช้ร่วมกับยากลุ่ม SYSADOA ได้

Consensus: NSAIDs can be used for up to 2 weeks for knee inflammation and can be used with SYSADOAs.

Delegate vote: Agree 94.2%, Disagree 4.35%, Abstain 1.45% (Strong Consensus)

Justification: NSAIDs have been traditionally indicated as an effective treatment in pain relief and functional improvement in patients with knee OA. Many clinical practice guidelines, such as the AAOS[41], OARSI[130], and ACR[101], provide strong evidence supporting the use of NSAIDs as an initial analgesic therapy. However, the long-term use of NSAIDs has been associated with a variety of potentially serious adverse events, including gastrointestinal hemorrhaging and kidney dysfunction. Limiting the dosage of NSAIDs may decrease the incidences of these adverse events.[131-134] Our consensus group recommends that practitioners prescribe oral NSAIDs, including COX-2 inhibitors, to be taken orally at low doses for short periods of time (no more than 2 weeks) for patients with knee OA.

SYSADOAs, including glucosamine sulphate, chondroitin sulphate, and diacerein, decrease OA symptoms with a slow onset of action that may delay the progression of changes in joint structure, along with symptom modifications (disease-modifying effects); different levels of evidence support the difference classes of drugs within this group.[27,135] In theory, SYSADOAs should also be able to decrease the consumption of NSAIDs for prolonged symptom control and/or for OA flares. Some research provides evidence on the positive treatment effects of using a combination of SYSADOAs and NSAIDs.

The PEGASus study[136] was designed to assess the impact of SYSADOAs on the use of NSAIDs in 745 patients with knee OA to further assess the efficacy of this drug class and to substantiate the public health's interest in the prevention of risks induced by NSAIDs. They concluded that crystalline glucosamine sulphate was the only SYSADOA that corresponded with a decrease in NSAID use. Nevertheless, it is difficult to interpret the lack of effect in decreased NSAID consumption

found with other SYSADOAs. The recent ESCEO study[27] recommended only the use of prescription formulations of glucosamine sulphate (i.e., the patented crystalline glucosamine sulphate described previously) or chondroitin sulphate as the first step of treatment and for prolonged use in the treatment of patients with knee OA, as the evidence is scarce for other SYSADOAs, such as diacerein. Although there is inadequate evidence on the efficacy of other SYSADOAs, our consensus group has no reason to argue against the use of SYSADOAs in combination with NSAIDs.

คำถามที่ 21: ยากลุ่ม NSAIDs สามารถใช้ในการรักษาผู้ป่วยข้อเข่าเสื่อมในการควบคุมอาการปวดได้นานเท่าไร?

Question 21: How long should NSAIDs be used for pain control in patients with knee OA?

ความเห็นร่วม: ยากลุ่ม NSAIDs สามารถใช้ในการรักษาผู้ป่วยข้อเข่าเสื่อมในการควบคุมอาการปวดได้เป็นระยะๆ ด้วยความระมัดระวัง

Consensus: NSAIDs should only be used for a short-term period and intermittently, with caution and the patient's comorbid conditions taken into account.

Delegate vote: Agree 100%, Disagree 0%, Abstain 0% (Unanimous Consensus)

Justification: NSAIDs are a class of drugs that are commonly recommended to relieve pain and to improve function in patients with OA.[137,138] However, the effect of continuous use is still controversial due to the lack of supporting evidence. In addition, other complications, such as GI bleeding, renal insufficiency, bleeding disorders and cardiovascular risks, are

major causes of concern; physicians should therefore be aware of how long to prescribe these drugs and their duration use.[137]

Osani et al. recently performed a meta-analysis that collected data from 64 RCTs. They found that NSAIDs showed a strong efficacy in pain relief and improved function during 2-12 weeks after administration. At 26 weeks after administration, these effects were diminished. This study recommended the discontinuation of NSAIDs beyond 12 weeks due to the lack of supporting data on its efficacy. A previous RCT study by Scott et al.[138] reached a similar conclusion and recommended only 2-4 weeks.

คำถามที่ 22: ยากลุ่ม COX-2 inhibitor สามารถใช้ในการรักษาผู้ป่วยข้อเข่าเสื่อมได้โดยเฉพาะในผู้ป่วยที่มีผลข้างเคียงทางระบบทางเดินอาหารจากการใช้ยากลุ่ม NSAIDs ทั่วไป

Question 22: Can COX-2 inhibitors be used for knee OA in high-risk patients with GI issues that can be worsened with conventional NSAIDs?

ความเห็นร่วม: ใช่

Consensus: Yes

Delegate vote: Agree 98.55%, Disagree 1.45%, Abstain 0% (Strong Consensus)

Justification: NSAIDs bind to the COX enzyme, blocking the conversion of arachidonic acid to prostaglandins; this is most likely the main mechanism for their anti-inflammatory and analgesic effects. The COX-1 isoform of the enzyme is expressed in many normal tissues. Prostaglandins produced by COX-1 play an important role in normal tissue hemostasis,

such as in mucosal defense and repair in the GI system.[139, (140)] The COX-2 isoform, although found in normal tissue, is also an inducible enzyme and appears in areas of inflammation and injury.[(141)]

Conventional NSAIDs were nonselective, in that they bound to and inhibited the COX-1 and COX-2 isoforms. Selective COX-2 inhibitors, such as celecoxib and etoricoxib, were developed to avoid the adverse effects associated with non-specific COX inhibition.

Selective COX-2 inhibitors are associated with a lower risk of adverse GI events and complications.[(140,142)] Two large prospective, randomized outcome studies were performed for celecoxib and etoricoxib.[(143,144)] Celecoxib was compared with diclofenac and ibuprofen; etoricoxib was compared with diclofenac. The risk of symptomatic ulcers or ulcer complications were lower with the selective COX-2 inhibitors than other drugs.

คำถามที่ 23: ยา NSAIDs กลุ่ม selective COX-2 inhibitor สามารถลดอาการปวดในผู้ป่วยข้อเข่าเสื่อมได้ดีกว่ากลุ่ม conventional NSAIDs หรือไม่

Question 23: Is the COX-2 inhibitor superior to conventional NSAIDs for pain control in patients with knee OA?

ความเห็นร่วม: ไม่

Consensus: No

Delegate vote: Agree 82.61%, Disagree 13.04%, Abstain 4.35% (Strong Consensus)

Justification: Managing OA pain is based on a sequential hierarchical approach, with NSAIDs as the main form of treatment.[122,123] In the US, about 65% of patients with OA are prescribed NSAIDs, making them one of the most widely used drugs in this patient population.[124]

Jevsevar et al.[20] reported a network meta-analysis to determine the clinical efficacy of several drug treatments, including NSAIDs, acetaminophen, IA corticosteroids, IA PRP, and IA HA, by comparing them with each other, as well as with oral and IA placebos.[20] For pain management, all active treatments had higher efficacy than oral placebos. In terms of function, celecoxib, diclofenac, and ibuprofen had statistically higher significance and the "potential to be clinically significant" efficacy than oral placebos, with an increasing effect on function due to their large statistically different magnitudes of effect (0.82 [0.65 to 1], 0.88 [0.56 to 1.2], and 0.66 [0.17 to 1.15], respectively). Naproxen was the only treatment that showed clinical significance when compared with an oral placebo. Overall, naproxen was found to be the most effective single treatment for decreasing pain and improving function.

Da Costa et al.[14] reported a network meta-analysis showing that diclofenac, at a maximum daily dose of 150 mg/day, was most effective for the treatment of pain and physical disability in OA, with a higher efficacy than the maximum doses of frequently used NSAIDs, including ibuprofen, naproxen, and celecoxib. Etoricoxib, at a dose of 60 mg/day, was as effective as diclofenac at 150 mg/day for the treatment of pain, however, its effect estimates on physical disability were inconclusive.

คำถามที่ 24: สามารถใช้ยากลุ่ม NSAIDs ร่วมกับ กลุ่ม weak opioids ในการรักษาผู้ป่วยข้อเข่าเสื่อมได้หรือไม่

Question 24: Can the combination of NSAIDs and weak opioids be used in the treatment of knee OA?

ความเห็นร่วม: สามารถใช้ยากลุ่ม NSAIDs ร่วมกับ กลุ่ม weak opioids ในการรักษาผู้ป่วยข้อเข่าเสื่อมได้ในการลดภาวะแทรกซ้อนจากขนาดของยาแต่ละชนิด

Consensus: The combination of NSAIDs and weak opioids can be used in treating knee OA, leading to a reduction in the dosage of each drug that and can decrease the amount of side effects.

Delegate vote: Agree 100%, Disagree 0%, Abstain 0% (Unanimous Consensus)

Justification: The goal of analgesic therapy in chronic painful OA is symptomatic relief, thereby allowing patients to continue routine activities of daily living.[145,146] NSAIDs are commonly recommended as the initial analgesic therapy drug[41] and many patients who are prescribed NSAIDs enjoy pain relief, with no intolerable side-effects. However, the long-term use of NSAIDs has been associated with a variety of potentially serious side-effects, including gastrointestinal hemorrhaging and kidney dysfunction. Limiting the dosage of an NSAID may decrease the number of side-effects.[131-134]

An accumulating body of evidence indicates that NSAIDs and weak opioids (e.g., tramadol and codeine) produce analgesia through different mechanisms. NSAIDs act mainly in the periphery, binding to the COX enzyme, and blocking the conversion of arachidonic acid to prostaglandins; this is

the likely main mechanism for their anti-inflammatory and analgesic effects. Opioids, such as tramadol, act mainly in the central, with at least two modes of action that may contribute towards its efficacy, e.g., binding to the mu-opioid receptors and inhibiting norepinephrine and serotonin reuptake.[131] These drugs are used in the treatment of moderate-to-moderately severe pain.

Schniter et al.[147] reported a double-blind randomized placebo-controlled study with 236 patients receiving a combination of naproxen and tramadol or naproxen and a placebo for OA pain. This study found that tramadol decreased the amount of naproxen needed to maintain adequate pain relief in naproxen-responsive patients with painful knee OA. The addition of tramadol at 200 mg/day allowed for a mean reduction of 78% in the daily dose of naproxen without compromising pain relief. However, 20% of patients taking tramadol with naproxen dropped out due to adverse events, compared with 13% of patients taking the placebo and naproxen. The side-effects that led to withdrawal (nausea, vomiting, and dizziness) are similar to those experienced in other studies of tramadol.

คำถามที่ 25: ยากลุ่มสเตียรอยด์ชนิดรับประทานสามารถใช้เป็นตัวเลือกหนึ่งในการใช้รักษาผู้ป่วยข้อเข่าเสื่อมได้หรือไม่

Question 25: Are oral steroids (e.g., prednisolone) appropriate for pain control as an alternative drug in patients with knee OA?

ความเห็นร่วม: ไม่มีข้อมูลเพียงพอในการใช้ยากลุ่มสเตียรอยด์ชนิดรับประทานในการรักษาผู้ป่วยข้อเข่าเสื่อม

Consensus: There is not enough evidence to support the treatment of knee OA with oral steroids.

Delegate vote: Agree 85.51%, Disagree 7.25%, Abstain 7.25% (Strong Consensus)

Justification: OA is a progressive disease caused by the failed repair of joint damage that, in the preponderance of cases, has been triggered by abnormal intraarticular stress. OA is considered a complex, multifactorial disease, with patients found in a heterogeneous patient population exhibiting varying degrees of inflammation that are, in some cases, comparable with RA.[148-150]

Inflammation may be the cause of symptoms and the progression of OA. In patients with OA, it is recognized that low-grade synovial inflammation is often present and correlates with pain severity and progressive cartilage degeneration.[151,152] Indeed, inflammation may be the crucial link between local noxious stimuli and the recruitment of centrally mediated pathways. When inflammatory mediators, such as interleukin 1β (IL-1β) and tumor necrosis factor (TNF)-α, are released intra-articularly from damaged tissue, they can modulate both central and peripheral nociceptors.

Corticosteroids have direct and indirect roles in minimizing the production/release of cytokines by inhibiting phospholipase A2 and the ensuing arachidonic acid metabolic pathway. This proposed mechanism results in decreased inflammation and in reduced pain expression. Additionally, corticosteroids enhance the inhibition of transcription factors (e.g., NK-KB), resulting in the subsequent decreased expression of pro-inflammatory genes; however, whereas upon binding to glucocorticoid responsive elements (GREs) adjacent to promoters of anti-inflammatory genes, corticosteroids increase the expression of the latter. However, currently, no clinical evidence supports the use of corticosteroids in the treatment of knee OA.

Although systemic corticosteroids remain an important component of therapy for many conditions, there are arguments against their use, mainly based around concerns of toxicity. Systemic corticosteroids can cause suppression of the hypothalamic-pituitary-adrenal (HPA) axis[153] and is associated with an increased risk of complications related to infections. The chronic administration of high doses of corticosteroids is the most common cause of adrenal insufficiency and Cushing's syndrome.

In conclusion, there is no adequate evidence that supports or is against the use of oral steroids in patients with knee OA, with the need for additional studies.

คำถามที่ 26: ยากลุ่ม SYSADOA สามารถใช้ในการรักษาผู้ป่วยข้อเข่าเสื่อมชนิดทุติยภูมิหรือไม่?

Question 26: Do SYSADOAs have a role in the secondary treatment of knee OA?

ความเห็นร่วม: ใช่

Consensus: Yes

Delegate vote: Agree 73.91%, Disagree 14.49%, Abstain 11.59% (Strong Consensus)

Justification: The cause of secondary osteoarthritis of the knee is multifactorial factors such as injury, infection, and inflammatory disease. As well as sports participation-injury to the joint, life-style and obesity may predispose younger generation to develop early osteoarthritis.[154] There have been reports of increasing in the incidence of total joint replacement not only in elderly patients (> 65 years) but also in younger patients

(< 65 years).[155] As for the indications for lower extremity joint arthroplasty have been extend to include both younger and more active patients. Life-style and strenuous physical demands in young patients may shorten longevity of knee prosthesis and may be lead to early on revision.

O. Bruyere et al. report long-term study of 275 patients with knee OA whose underwent the treatment of oral glucosamine sulphate 1,500 mg once-a-day for at least 12 months and up to 3 years in two previous randomized, placebo-controlled, double-blind trials.[156,157] They report a lower incidence of total joint replacement (p = 0.026) during an average follow-up of further 5 years in the treatment group after drug discontinuation, compared with patients who had received placebo.[100]

Reginster JY et al. report no significant joint-space loss in the patients with osteoarthritis knee who's randomly treated by 1,500 mg glucosamine sulphate daily for 3 years. As for the placebo group, progressive joint-space narrowing could be observed on anteroposterior radiographs of each knee in full extension. According to the study, glucosamine sulphate may suggest to be disease and structural modifying of osteoarthritis.[158]

คำถามที่ 27: ยากลุ่มสเตียรอยด์ชนิดรับประทาน สามารถใช้ในการรักษาผู้ป่วยข้อเข่าเสื่อมชนิดทุติยภูมิหรือไม่?

Question 27: Do oral steroids have a role in the secondary treatment of knee OA?

ความเห็นร่วม: ใช่

Consensus: Yes

Delegate vote: Agree 63.77%, Disagree 15.94%, Abstain 20.29% (Weak Consensus)

Justification: OA is a progressive disease resulting from the failed repair of joint damage that, in the preponderance of cases, has been triggered by abnormal intra-articular stress. OA is considered a complex, multifactorial disease, with patients from a heterogeneous patient population that exhibits varying degrees of inflammation, which are, in some cases, comparable with RA or crystal-induced arthritis.[148-150]

Corticosteroids mimic the effects of hormones naturally produced from the adrenal glands, which are the small glands that sit on top of the kidneys. When prescribed in doses that exceed the body's usual levels, corticosteroids can suppress inflammation. This can reduce the signs and symptoms of inflammatory conditions, such as arthritis and asthma. Corticosteroids also suppress your immune system, which can help control conditions in which your immune system mistakenly attacks its own tissues, such as in autoimmune disorders.

Although systemic corticosteroids remain an important component of therapy for many conditions, there are arguments against their use, mainly based on concerns regarding their toxicity. Systemic corticosteroids can suppress HPA-axis function[153] and is associated with an increased risk of infectious complications. The chronic administration of high doses of corticosteroids is the most common cause of adrenal insufficiency and Cushing's syndrome. Due to these side-effects, corticosteroids should be used with caution and monitored by rheumatologists.

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กลุ่มที่

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ยารักษาข้อเข่าเสื่อมชนิดฉีดเข้าข้อและใช้ภายนอก
Non-oral and topical medications for osteoarthritis of the knee

รายชื่อกลุ่ม 2
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ประธานกลุ่ม	Chairman
พ.ท. นพ.สารเดช เขื่องศิริกุล	Lt. Col. Saradej Khuangsirikul, MD.

ตัวแทนกลุ่ม	Delegates
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รศ. นพ.สุพิชัย เจริญวารีกุล	Assoc. Prof. Supichai Charoenvareekul, MD.
รศ. นพ.ปิยะ ปิ่นศรศักดิ์	Assoc. Prof. Piya pinsornsak, MD.
รศ. นพ.บุญชนะ พงษ์เจริญ	Assoc. Prof. Boonchana Pongcharoen, MD.
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Session 2: ยารักษาข้อเข่าเสื่อมชนิดฉีดเข้าข้อและใช้ภายนอก
Non-oral and topical medications for osteoarthritis of the knee

คำถามที่ 1: ประโยชน์ของการฉีดสเตียรอยด์เข้าข้อมีอะไรบ้าง

Question 1: What are the benefits of intra-articular corticosteroids?

ความเห็นร่วม: ลดอาการปวด เพิ่มสมรรถนะการใช้งานในระยะสั้น (12 สัปดาห์) ลดการบวมและการอักเสบ

Consensus: To improve pain and function, during a short-term period (within 12 weeks), and to decrease swelling and inflammation.

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous Consensus)

Justification: The efficacy of corticosteroids in knee OA has been evaluated in several studies. In 2003, EULAR[1] recommended an intra-articular injection of long-acting steroids to treat the acute exacerbation of knee pain, especially when accompanied by an effusion (evidence 1B). However, its prescribed use can only reduce pain and inflammation and improve functional outcomes during a short-term period.[1] Based on two systematic reviews, OARSI also recommended intra-articular corticosteroids as an appropriated treatment for knee OA as it demonstrated a clinically significant short-term decrease in pain.[2]

A recent Cochrane review from 2015,[3] that included 27 RCTs (n=1,767 patients), revealed that intra-articular corticosteroids can improve pain and function over a short-term

period. For pain reduction, a moderate effect at 1-2 weeks was shown, with small to moderate effects at 4-6 weeks, a small effect at 13 weeks, and no evidence of effect at 26 weeks. In terms of functional improvement, intra-articular corticosteroids have a small to moderate effect at 1-2 weeks, a small to moderate effect at 4-6 weeks, and no evidence of effect at 13 weeks. Nevertheless, the overall quality of evidence, combined with the considerable heterogeneity between trials, were problematic in this meta-analysis. Finally, a recent network meta-analysis[4] of 129 trials (n=32,129 patients) on the pharmacological treatment of knee OA revealed that intra-articular corticosteroids are superior to intra-articular placebos and all other oral treatments.

คำถามที่ 2: ข้อบ่งชี้ในการฉีดสเตียรอยด์เข้าข้อมีอะไรบ้าง

Question 2: What are the indications for intra-articular corticosteroids?

ความเห็นร่วม: ข้อเข่าเสื่อมระยะปานกลางขึ้นไป โดยเฉพาะผู้ป่วยที่มีการอักเสบเฉียบพลัน น้ำในข้อมาก ปวดเมื่อไม่ใช้งาน มีข้อห้ามในการใช้ยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์ มีข้อห้ามในการผ่าตัดหรือปฏิเสธการผ่าตัด ไม่ได้ผลจากการใช้ยาชนิดรับประทานและยาทา

Consensus: In moderate to severe OA knee (especially in patients with acute inflammation, effusion, or resting pain), indications for IA corticosteroids include contraindication to oral NSAIDs, contraindication or refusal to surgery, or failed oral or topical medications.

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous Consensus)

Justification: Tian et al.[5] conducted a literature review by performing electronic searches in Medline (1966-2017.11), PubMed (1966- 2017.11), Embase (1980-2017.11), ScienceDirect (1985-2017.11), and the Cochrane Library (1900-2017.11) for RCTs comparing the use of methylprednisolone in the treatment of knee OA. The primary outcomes were the WOMAC pain scores and WOMAC function scores. They concluded that IA methylprednisolone injections were associated with improved pain relief and physical function in patients with knee OA. Additionally, no severe adverse effects were observed. However, due to the limited quality and amount of evidence currently available, higher quality RCTs are still required.

In 2014, the NICE 2014 strongly agreed with the use of IA corticosteroid injection, which could be prescribed in adjunction to core treatments for the relief of moderate-to-severe pain in knee OA.

In 2012, the ACR 2012 suggested that IA corticosteroid injections can be used during OA treatments at a conditionally recommended level (i.e., in that there was no high quality evidence and/or only a small amount of evidence on the advantages and disadvantages of IA corticosteroid injections).[6]

In 2003, the EULAR had several suggestions on the management of knee OA. They found that IA corticosteroids had a level of evidence at IB and a strength of recommendation A (Table 1). Additionally, intra-articular injections of long-acting corticosteroids are recommended during knee pain flare-ups and especially if accompanied by an effusion.[1]

Table 1. Level of evidence based on a literature search (selected only evidence level 1).

Intervention	Level of evidence	Range of Effect sizes	Strength of recommendation
Acetaminophen	1B		A
Opioid	1B		B
NSAIDs			
Conventional NSAID	1A	0.47-0.96	A
Coxibs	1B	0.5	A
Topical NSAID	1A	-0.05-1.03	A
Topical capsaicin	1A	0.41-0.56	A
SYSADOA			
Glucosamine	1A	0.43-1.02	A
Chondroitin	1A	1.23-1.50	A
Diacerein	1B		B
Education	1A	0.28-0.35	A
Exercise	1B	0.57-1.0	A
Acupuncture	1B	0.25-1.74	B
Laser	1B	0.87	B
Spa therapy	1B	1.0	C
TENS	1B	0.76	B
Ultrasound	1B		C
Weight loss	1B		B
Insoles	1B		B
Orthotic device (knee brace/patella tape/elastic bandage)	1B		B
IA Hyaluronic acid	1B	0.0-0.9	B
IA Corticosteroid	1B	1.27	A

This table was modified from Table 5 of Jordan et al. EULAR Recommendation 2003 for the management of knee OA.

However, according to the AAOS in 2013 (the 2nd edition evidence-based guideline for OA of the knee), there appears to be inconclusive evidence on the use of IA corticosteroids for patients with symptomatic knee OA. Although research came from four placebo comparison studies that evaluated pain relief for a minimum treatment period of four weeks[7-10] only one study showed that IA corticosteroids were superior to placebos on the total WOMAC subscale scores at four weeks.[7]

We strongly agree with the use of IA corticosteroid injections for moderate-to-severe knee OA (especially in patients with acute inflammation, effusion, or resting pain), in contraindication to oral NSAIDs, in contraindication or refusal to surgery, and in cases of failed oral or topical medications.

คำถามที่ 3: สเตียรอยด์ชนิดใดบ้างที่สามารถใช้ฉีดเข้าข้อได้

Question 3: Which corticosteroids can be used in IA injections?

ความเห็นร่วม: Triamcinolone, methylprednisolone, betamethasone and dexamethasone

Consensus: Triamcinolone, methylprednisolone, betamethasone, and dexamethasone

Delegate vote: Agree: 85.51%, Disagree: 4.35%, Abstain: 10.14% (Strong Consensus)

Justification: Intra-articular inflammation of the synovium is a common finding in knee OA, with synovitis associated with pain. IA corticosteroid injections are a pharmacological

treatment that has been used for several decades to reduce inflammation and pain.

Five different steroids are approved by the FDA and can be given to treat knee OA, i.e., triamcinolone hexacetonide, methylprednisolone acetate, betamethasone acetate, triamcinolone acetate, betamethasone sodium phosphate, and dexamethasone.[11]

A large American survey revealed that more than 95% of rheumatologists use IA corticosteroid injections during knee OA treatment; however, there is still controversy on which is the most effective steroid preparation. Currently, intra-articular triamcinolone hexacetonide and methylprednisolone acetate are the most commonly used and studied preparations.[12]

Synthetic corticosteroids have a higher anti-inflammatory potency than native cortisol, and are derivatives of prednisolone, an analogue of human cortisol. Depo-medrol is the injectable formulation of methylprednisolone acetate, and the fluorinated derivatives of prednisolone are betamethasone, dexamethasone, and triamcinolone. Triamcinolone is frequently used as an injectable used for orthopedic conditions.[13] Methylprednisolone and triamcinolone are the two most common injectables used to treat knee OA. They have an equivalent potency; however, triamcinolone is less water-soluble. The average duration of benefit ranges from 8 to 56 days for methylprednisolone and 14 to 66 days for triamcinolone.[14-16]

Several studies have looked at the effects of corticosteroids, such as methylprednisolone and triamcinolone. Tian et al.[5] conducted a systematic review and meta-analysis and concluded that IA methylprednisolone injections were associated with improved pain relief and physical function in patients with knee OA.

A randomized, double-blinded, placebo-controlled, clinical knee OA-trial performed by Riis et al.[17] evaluated the effects of IA corticosteroids versus placebo injections using KOOS (knee injury and osteoarthritis outcome score). Synovitis was assessed on conventional non-contrast-enhanced, conventional contrast-enhanced (CE) and dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) scans. Improvements in pain and function following the IA corticosteroid injection could not be explained by a decrease in synovitis as seen on an MRI.

McAlindon et al.[18] assessed triamcinolone in their study to determine the effects of an IA injection of 40 mg of triamcinolone acetonide every 3 months on the progression of cartilage loss and knee pain. This study was a two-year, randomized, placebo-controlled, double-blind trial of IA triamcinolone versus saline for symptomatic knee OA with ultrasonic features of synovitis in 140 patients. IA triamcinolone was found to be associated with a significantly greater cartilage volume loss than saline. for a mean change in index compartment cartilage thickness of -0.21 mm versus -0.10 mm, respectively, with no significant differences in pain.

The guideline of the Brazilian medical association, following the standard of a systematic review with evidence retrieval based on evidence-based medicine, found a strong recommendation for IA corticosteroid injections, i.e., triamcinolone acetonide, triamcinolone hexacetonide, and methylprednisolone. There were no differences between infiltration with triamcinolone hexacetonide and methylprednisolone in pain relief for knee OA between 2 and 6 weeks. Infiltration with methylprednisolone was more effective in relieving pain than triamcinolone acetonide in patients with knee OA for a maximum of 6 weeks and was equally effective in the improvement

of function for up to 12 weeks. Triamcinolone hexacetonide may be favored over methylprednisolone based on the faster onset of action for pain relief. There were no differences in functional improvement for up to 24 weeks between IA injections of methylprednisolone and triamcinolone hexacetonide.

A randomized, double-blind study by Lomonte et al.[12] found that IA triamcinolone hexacetonide and methylprednisolone acetate injections were equally effective in terms of pain improvement and function. Pain relief and functional improvement were achieved after a single injection of both IA methylprednisolone acetate and triamcinolone hexacetonide and were sustained for as long as 24 weeks.

Yavuz et al.[19] performed a 12-week randomized, placebo-controlled trial that compared three IA corticosteroid preparations (triamcinolone acetonide, methylprednisolone, and betamethasone disodium phosphate) and found that methylprednisolone acetate had a higher analgesic effect than the other corticosteroids for at least six weeks.

Klocke et al.[20] used corticosteroid injections to study changes in biomarker levels in the cartilage and during bone metabolism after an injection. Eighty subjects with symptomatic knee OA underwent a routine knee joint injection with 40 mg of triamcinolone acetonide and 4 mL 1% of lignocaine. Knee pain WOMAC VAS and biomarkers were measured at baseline and 3 weeks after IA triamcinolone acetonide injection. No significant associations were found between baseline uCTX-II and changes in pain post-IACI. Additionally, there were no significant correlations between baseline uCTX-II and age, BMI, or gender.

Currently, there are many studies on IA steroid injections, with the most highly studied corticosteroids being methyl-

prednisolone acetate and triamcinolone acetonide. These studies show supporting evidence on the use these IA injections.

คำถามที่ 4: การฉีดสเตียรอยด์เข้าข้อมีผลกระทบต่อกระดูกอ่อนผิวข้อหรือไม่

Question 4: Do IA corticosteroids have an effect on the cartilage?

ความเห็นร่วม: การฉีดสเตียรอยด์เข้าข้ออาจมีผลต่อการสูญเสียปริมาณกระดูกอ่อนผิวข้อเมื่อใช้ต่อเนื่องในระยะยาว

Consensus: Yes, it may lead to the loss of cartilage volume with long-term use.

Delegate vote: Agree: 94.2%, Disagree: 4.35%, Abstain: 1.45% (Strong Consensus)

Justification: The effect of IA corticosteroids on cartilage is a main cause of concern for orthopedists. Several RCTs have compared IA triamcinolone versus saline on knee cartilage volume in patients with knee OA. McAlindon et al.[18] included 140 patients with OA and Kellgren-Lawrence Grades at levels 2 or 3 for severity. One group of patients were injected with 1 mL of triamcinolone (40 mg/mL); the other group received an injection of 1 mL of 0.9% sodium chloride. Both groups were injected with triamcinolone or normal saline every 12 weeks for 2 years. Cartilage loss was evaluated with a MRI at Months 0, 12, and 24, with a greater rate of cartilage thickness loss in the triamcinolone group.

Another RCT with a smaller sample size (n=68 patients) compared IA triamcinolone 40 mg and normal saline in patients with OA.[9] Both groups of patients received an injection

every 3 months for 2 years. However, this study did not find any radiologic differences between the treatment and control groups via a plain radiographic with a standardized radiographic protocol.[21]

Another study compared 53 patients with OA (n=82 knees) who did not receive corticosteroid injections with 8 patients (n=14 knees) who received IA steroids. The mean age of the patients at the beginning of the trial was 60 years, and 70 years at the end of the study. In the IA steroids group, the median number of corticosteroid injections per joint was 25. The results showed that radiographic degeneration was more advanced in the IA steroids groups than the control group in terms of femorotibial angle and grading of OA.[22]

There are various hypotheses on the deterioration of articular cartilage via IA steroid injections. The first hypothesis is that the analgesia effect of IA steroid injections might lead to the overuse of the knee, which subsequently results in higher rates of microtrauma. Another hypothesis is that the chondrotoxicity of steroids may have reported effects of chondrotoxicity that are dose-dependent.[23]

Based on previous clinical evidence, we agree that IA corticosteroids may lead to losses in cartilage volume with long-term use, especially with regular injections over 2 years.

คำถามที่ 5: ยาชาที่ผสมในสเตียรอยด์ฉีดเข้าข้อมีผลต่อกระดูกอ่อนผิวข้อหรือไม่

Question 5: Do local anesthetic agents that mixed with cortisone injections have an effect on knee cartilage?

ความเห็นร่วม: ยาชามีผลเสียต่อเซลล์กระดูกอ่อนผิวข้อ

Consensus: Yes, it has a chondrotoxic effect.

Delegate vote: Agree: 92.65%, Disagree: 2.94%, Abstain: 4.41% (Strong Consensus)

Justification: Local anesthetic agents are a typical favored substance that is mixed with corticosteroids for IA injections in patients with OA. However, many studies have reported the chondrotoxicity of local anesthetic agents.[24] although, the exact mechanisms of chondrotoxicity are not known.

One study mentioned that a local anesthetic agent may affect mitochondrial energetics, which can induce cell apoptosis or necrosis.[25] The other key factor that leads to the probable development of chondrocyte toxicity-induced by local anesthetics might be from a blockade of potassium channels, which leads to the accumulation of mitochondria DNA damage.[26]

A well-controlled clinical study on IA injections with local anesthetic agents on patients with OA is limited. However, there was a case report on knee chondrolysis over a four-month period after arthroscopic surgery, with the authors stating that the probable cause in the development of chondrolysis was most likely bupivacaine.[27]

Several *in vitro* and animal studies have reported that bupivacaine,[28] lidocaine,[29] mepivacaine,[24] and ropivacaine[24] show chondrotoxicity and decrease chondrocyte viability. However, the concentration of each local anesthetic agent had various effects on cartilage. No studies have shown a significant chondrotoxic effect at low concentrations of bupivacaine (0.0625%), ropivacaine (0.1-0.2%), and mepivacaine (0.5%).[30] However, low concentrations of lidocaine (0.5%) were reported to have a chondrotoxic effect.[26-31]

Based on the above evidence, we agree that local anesthetic agents have chondrotoxic effects, with lidocaine inducing a chondrotoxic effect event in low concentrations. However, there is limited evidence on the chondrotoxic effects of other local anesthetic agents at low concentrations. Still, a low volume of local anesthetic agents can be used with caution.

คำถามที่ 6: การฉีดสเตียรอยด์เข้าข้อในการรักษาข้อเข่าเสื่อมสามารถฉีดได้บ่อยเพียงใด

Question 6: How often can steroid injections be given in the treatment of knee OA?

ความเห็นร่วม: ในข้อเข่าเสื่อมระยะ KL 2-3 สามารถฉีดได้ห่างกันอย่างน้อย 3 เดือน ติดต่อกันไม่เกิน 2 ปี ในระยะ KL 4 ฉีดได้ตามความเหมาะสมขึ้นกับวิจารณญาณของแพทย์

Consensus: In patients classified under KL 2-3, injections can be given in at least 3-month intervals but should not be continued for up to 2 years. In KL 4, injections can be administered more frequently, dependent on the physician's opinion.

Delegate vote: Agree: 88.41%, Disagree: 8.7%, Abstain: 2.9% (Strong Consensus)

Justification: The duration and doses of IA steroid injections are still inconclusive, with different injection doses dependent on the physician's discretion. Only certain types of doses were shown to have any effect on patients. The long-term efficiency of steroid injections is not well-studied, with the duration of efficacy mostly shown at 3 months.

Juni et al.[3] performed a prospective, randomized, controlled study, comparing the effects of methylprednisolone, betamethasone, and triamcinolone. They found a positive

effect from of all three injections, with symptoms decreasing over 12 weeks.

Many studies have performed comparative studies on triamcinolone acetonide 40 mg, including an observational study by Hirsch et al.[32] This study looked at the accuracy of injection and short-term pain relief following an IA corticosteroid injection in knee OA.

A randomized, double-blind, 24-week study by Lomonte et al.[12] assessed the efficacy of triamcinolone hexacetonide and methylprednisolone acetate IA injections in knee OA. They used 40 mg of IA triamcinolone hexacetonide and 40 mg of methylprednisolone acetate. Symptomatic knee OA and Kellgren-Lawrence Grades 2 and 3 were randomized to each injection group. Evaluations were performed at 4, 12, and 24 weeks. Both IA injections were equally effective, with improvements in pain and function sustained for up to 24 weeks.

A guideline on the management of IA steroid injections in knee OA was performed by the Brazilian medical association. The study was comparison of methylprednisolone acetate (MA) and triamcinolone acetonide (TA) or triamcinolone hexacetonide (TH). Infiltration with MA is more effective in relieving pain than TA in patients with knee OA for a maximum of six weeks, and equally effective in the improvement of function for up to 12 weeks. There were no differences between infiltration with MA and TH in pain relief for knee OA between 4 and 24 weeks. There were no differences between knee infiltration with MA and TH when functional improvement was evaluated for up to 24 weeks in patients with OA.

In 2018, Conaghan et al.[33] reported a Phase-3, multicenter, double-blind, 24 week study on the efficacy of a single IA injection of new microsphere-based, extended-release

triamcinolone acetonide and standard triamcinolone acetonide crystalline suspension. They found that extended-release triamcinolone acetonide provided significant and clinically meaningful pain reduction when compared to a saline-solution placebo at Week 12.

A systematic review and network meta-analysis on pharmacological treatments for knee OA, that included 129 trials (n=32,129 participants), found that for treating OA-related knee pain at 12 weeks, the effect size (ES) was superior for IA CS than IA placebo (ES = 0.32, 95% CI 0.16-0.47), oral placebo (ES = 0.61, 95% CI 0.32–0.89), oral acetaminophen (ES = 0.42, 95% CI 0.12–0.73) and all other oral treatments and was among the highest of all the pharmacological treatments assessed.[4]

A clinical trial[19] was conducted comparing the efficacy of several IA steroidal agents, including methylprednisolone acetate (40 mg, 1 mL), betamethasone disodium phosphate (3 mg, 1 mL), triamcinolone acetonide (40 mg, 1 mL), and serum physiological (0.09% NaCl, 1 mL). The study included 120 patients with painful knee OA. Evaluations on pain and functional index were performed before and after the 1st, 3rd, 6th and 12th weeks. The results showed that single doses of the three agents provided symptomatic and functional relief, with their effects reduced after the 12th week.

McAlindon et al.[18] performed a randomized clinical trial on the effect of IA triamcinolone and saline on knee cartilage volume and pain in patients with knee OA. They randomized 140 symptomatic OA knees with Kellgren-Lawrence Grades 2 and 3 into two groups, with IA injections of either 40 mg of triamcinolone acetonide or saline every 3 months for 2 years. IA triamcinolone injections resulted in significantly greater

cartilage volume loss than saline, with a mean change in index compartment cartilage thickness of -0.21 mm vs -0.10 mm and no significant differences in pain.

คำถามที่ 7: ประโยชน์ทางคลินิกของการฉีดน้ำข้อเทียม (hyaluronic acid) มีอะไรบ้าง

Question 7: What are the clinical benefits of IA hyaluronic acid?

ความเห็นร่วม: ลดอาการปวด เพิ่มสมรรถนะการใช้งาน ลดความฝืดของข้อ และประวิงเวลาในการเข้ารับการผ่าตัด

Consensus: Benefits include a reduction in pain, improved function, reduced stiffness, and a delay in surgery.

Delegate vote: Agree: 95.65%, Disagree: 1.45%, Abstain: 2.9% (Strong Consensus)

Justification: Hyaluronic acid (HA) is a prototype from the family of glycosaminoglycans found in many extracellular tissue, synovial fluid, and cartilage. In patients with OA, synovial HA becomes depolymerized, which results in decreased molecular weight and viscoelasticity, with increased susceptibility to cartilage injury.[34] Many studies have shown that IA injections of HA can decrease symptoms related to OA of the knee, with significant improvements in pain, functional outcomes, and reductions in stiffness, with few adverse events (VAS score, WOMAC score).[35-39] Some studies have shown the effectiveness of HA injections in delaying the time until total knee replacements (TKR). A retrospective study was conducted in the US which included 182,022 patients with knee OA knee who required TKR.[9] Patients experienced dose-dependent

differences in time delays until TKR was required: patients who received no HA had a median time-to-TKR of ~0.3 years; with one course of HA, the median time to TKR was >1.0 year; and patients who received 5 courses were delayed 3.6 years.

คำถามที่ 8: ข้อบ่งชี้ในการฉีดน้ำข้อเทียมมีอะไรบ้าง

Question 8: What are the indications to administer IA HA?

ความเห็นร่วม: รักษาด้วยยาแก้ปวดแล้วไม่ได้ผล หรือมีข้อห้ามในการใช้ยาแก้ปวดร่วมกับข้อใดข้อหนึ่งต่อไปนี้

1. ข้อเข่าเสื่อมระยะ KL 2-3
2. ข้อเข่าเสื่อมระยะ KL 4 ที่ปฏิเสธการผ่าตัด
3. มีข้อห้ามในการใช้ยาลดอักเสบที่ไม่ใช่สเตียรอยด์
4. มีข้อห้ามในการผ่าตัด

Consensus: Patients where analgesic medical treatments failed to work, or for patients that are unable to take analgesic medication with the following conditions:

1. OA knee with KL 2-3
2. KL 4 with refusal for surgery
3. Contraindication for NSAIDs
4. Contraindication for surgery

Delegate vote: Agree: 92.75%, Disagree: 2.9%, Abstain: 4.35% (Strong Consensus)

Justification: Intra-articular hyaluronic acid (IA HA) has several therapeutic benefits, with numerous meta-analyses (MAs) recently published and commentaries that highlight new evidence on the role of IA HA therapy in treating knee OA. The outcomes from eight MAs were reviewed comparing IA HA therapy with IA placebos or controls, with consistent and

statistically significant improvements shown for pain, function, and stiffness for up to 26 weeks. IA HA therapy is a well-tolerated and effective option for patients with mild-to-moderate knee OA when first-line pharmacological therapies have failed.[39]

The exact indications for viscosupplementation are still evolving; however, it can currently be considered for use in patients who have significant residual symptoms despite traditional non-pharmacologic and pharmacologic treatments. Additionally, patients who are intolerant of traditional treatments (e.g., gastrointestinal problems related to anti-inflammatory medications) are prime candidates for these injections.[40]

Table 2. Recommendations for the use of intra-articular hyaluronic acid in the management of knee osteoarthritis.

Organization	Recommendation
AAOS (2013)	Recommends against use. (recommendation is based on the lack of evidence supporting its efficacy, and not on its potential harm).[41]
ACR (2012)	Does not recommend it in the initial management of the disease. Conditionally recommends it in patients with no satisfactory response to prior recommended treatments.[6]
ESCEO (2014)	Recommends it in patients who are severely symptomatic, or still symptomatic, despite the use of NSAIDs, or in cases with contrain-dications to NSAIDs (Step 2).[42]
EULAR (2003)	Recommends it for pain reduction and functional improvement.[1]
NICE (2014)	Recommends not offering it.
OARSI (2014)	Recommends it only after a physician-patient interaction to determine whether it can be effective based on the patient's individual characteristics, comorbidities, and preferences (based on an uncertain appropriateness).[2]

คำถามที่ 9: ผู้ป่วยกลุ่มใดที่ไม่ควรได้รับการรักษาด้วยน้ำข้อเทียม
Question 9: Which patients should not receive IA HA?

ความเห็นร่วม: สงสัยภาวะติดเชื้อในข้อ ผิวหนังหรือเนื้อเยื่อข้างเคียงมีประวัติแพ้น้ำข้อเทียมหรือส่วนประกอบ และมีประวัติการรักษาด้วยน้ำข้อเทียมไม่ได้ผล

Consensus: Those with suspected septic arthritis, active skin or soft tissue infections, known hypersensitivity to hyaluronate preparations, and a history of unsuccessful IA HA injections.

Delegate vote: Agree: 98.55%, Disagree: 0%, Abstain: 1.45% (Strong Consensus)

Justification: IA knee injections are not recommended in cases with suspected knee infections, or skin infections in the area of the injection site, to reduce the potential for developing septic arthritis. Patients with a known history of hypersensitivity to hyaluronate preparations should also avoid IA HA injections. Serious side effects, such as pseudo-septic reactions and joint infections, have been reported, but at relatively low incidences.[43,44]

Other minor adverse effects and general tolerance include transient local reactions at the injected joint, which are observed at a rate of 2 to 4%.[45-47] In the treatment guidelines for knee OA, there have been some controversies regarding recommendations on IA HA injections. IA HA recommendations for knee OA in the OARSI guidelines are currently uncertain and was judged to be an inappropriate treatment option for multi-joint OA. The AAOS guidelines recommends against the use of HA for knee OA, as do the NICE 2014 guidelines for OA, which states that IA HA injections should not be offered in the management of OA.[41] However, the Cochrane Collaboration concluded that evidence was sufficient to support the use of HA in the treatment of knee OA, with a comparable efficacy seen with systemic interventions.[48]

In the consensus group, we strongly do not recommend the use of IA HA in patients with a history of unsuccessful IA HA injections.

คำถามที่ 10: ระยะเวลาที่สั้นที่สุดที่สามารถฉีดน้ำข้อเทียมซ้ำได้คือเท่าไหร่

Question 10: What is the minimum interval period for repeated courses of HA injections?

ความเห็นร่วม: 6 เดือน

Consensus: 6 months

Delegate vote: Agree: 94.2%, Disagree: 2.9%, Abstain: 2.9% (Strong Consensus)

Justification: HA is not a rapidly acting agent, but rather, its clinical effect on pain and function have a carryover effect that extends for a long period of time after administration. A recent analysis on 29 studies (n=4,866 participants) approved IA HA injections versus placebo and found a large treatment effect on knee pain and function when compared to pre-injection values from 4 to 26 weeks.[49] In other observational studies, IA HA injections in knee OA were highly effective and were shown to improve resting and walking pain, with up to 6 months duration of symptom control, and a reduction in concomitant analgesia use of up to 30-50%. Additionally, few adverse events were reported and were mostly limited to mild or moderate local adverse events of transient pain and swelling.[49,50] A therapeutic trajectory of IA HA versus placebo found that IA HA is effective after 4 weeks (ES=0.31; 95% CI: 0.17–0.45), reaching a peak in effectiveness at 8 weeks (ES=0.46, 95% CI: 0.28–0.65), and with a residual detectable effect on knee OA pain at 6 months post-intervention (ES=0.21, 95% CI: 0.10–0.31)[49] A systematic review and meta-analyses comparing IA HA treatment with other IA therapies and oral

NSAIDs concluded that HA is a viable treatment option for knee OA, producing improvements in pain and function that can persist for up to 26 weeks, and demonstrated a good safety profile.[50]

คำถามที่ 11: น้ำข้อเทียมที่มีน้ำหนักโมเลกุลที่ต่างกันมีประโยชน์ในการรักษาต่างกันหรือไม่

Question 11: Does HA with different molecular weights provide different benefits in treating knee OA?

ความเห็นร่วม: ไม่สามารถสรุปได้ มีหลักฐานอย่างจำกัดว่าน้ำข้อเทียมที่มีน้ำหนักโมเลกุลสูงมีผลทางคลินิกที่เหนือกว่า

Consensus: The results are inconclusive, there is a limited amount of evidence on the superiority of high molecular weight HA in clinical studies.

Delegate vote: Agree: 89.86%, Disagree: 5.8%, Abstain: 4.35% (Strong Consensus)

Justification: Overall, HA has shown good clinical outcomes,[51-54] with patients experiencing a reduction in pain and improved function after an injection.[54-57]

However, a high molecular weight hyaluronic acid (HMWHA) has nearly the same molecular weight as natural HA.[58] Therefore, a HMWHA may be better than a low molecular weight hyaluronic acid (LMWHA) due to several mechanical properties, such as better lubrication, higher shock absorption, and a longer retainment in the joint.[59-61]

Moreover, a HMWHA also stimulates chondrocyte cells and synoviocyte cells better than a LMWHA.[59,61,62] Therefore, a HMWHA should be more effective in terms of long-term pain

control. However, three studies found similar VAS for pain and functional scores between HMWHA and LMWHA.[54,63,64] Additionally, only one RCT study has shown that HMWHA has a statistically significant lower VAS for pain and a higher functional score than LMWHA.[61] However, this study did not inject a placebo in the HMWHA group, with three injections for HMWHA and five injections for LMWHA. Therefore, the higher pain score and worst functional outcomes may be due to injection site complications.

In conclusion, although previous studies have shown that HMWHA has a lower VAS for pain and a better functional outcome after injection, almost all of these studies were not statistically significant, apart from only one RCT. Therefore, more studies are still needed to prove the efficacy of HMWHA.

คำถามที่ 12: การฉีดสเตียรอยด์ร่วมกับน้ำข้อเทียมมีประโยชน์ทางคลินิกหรือไม่

Question 12: Does steroid use combined with viscosupplements have any clinical benefits?

ความเห็นร่วม: ไม่สามารถสรุปได้

Consensus: The results are inconclusive.

Delegate vote: Agree: 86.96%, Disagree: 5.8%, Abstain: 7.25% (Strong Consensus)

Justification: HA and IA corticosteroid injections have both demonstrated efficacy in the management of knee OA in well-designed randomized controlled trials.[48,2] Numerous trials have demonstrated the ability of corticosteroid injections to alleviate pain within the first 2-4 weeks post-injection; however, these

effects diminish over time. HA injections require a longer time to see any pain relief effects, at almost 4 week and up to 3 months; however, these effects are long-lasting.[65,66]

While both interventions have limitations when administered separately, their combination in the management of OA may provide improved symptomatic relief for certain patients. Several trials have investigated a combined intervention of IA injections of corticosteroid and HA in comparison to more traditional monotherapies of either IA injections of HA alone or IA injections of corticosteroid alone.

A meta-analysis was performed by Smith et al.[67] on IA injections, including either combined corticosteroid and HA or HA alone. There were no significant differences in WOMAC total scores (SMD=-0.02; 95% CI: -0.35-0.30); (n.s.), P=0.88, I2=13%) and OMERACT-OARSI responder rates (OR=1.17; 95% CI: 0.60-2.26); (n.s.), P=0.65, I2=0%).[67]

In a 1-year follow-up, randomized, single-blind trial that looked at combined treatments of HA and corticosteroid versus HA treatments alone. Ozturk et al. found: that improve ments in ROM were not significantly different for all patients - ($p>0.05$); WOMAC questionnaires significantly improved only at the second month following treatment in the combined group ($p<0.05$), but were not significant in the other months of evaluation during the study ($p>0.05$); and that stiffness, as assessed by the WOMAC, also did not show any significant differences between groups ($p>0.05$).[68]

In a randomized controlled trial by Wang et al.,[69] researchers evaluated a single shot co-injection of HA and corticosteroid compared with the use of HA alone. Following treatment, the VAS scores in the HA & corticosteroid group decreased significantly when compared with the HA group

at Week 1, Month 1, and Month 3 (P<0.05). At Month 6, the mean VAS scores in both groups were not significantly different. Improved WOMAC scores, in terms of pain, stiffness and physical function, and better knee function, were observed in the HA & corticosteroid group when compared with the HA group during the first 3 months post-injection (P<0.05). However, no significant differences were observed between groups at Month 6. In terms of the active flexion motion of the knee, both groups reported improved flexion compared with the baseline for the first 3 months post-injection. No significant differences in mean flexion angle of the knee were observed between groups at any time point.[69]

Campos et al.[70] performed a RCT that found that adding triamcinolone improved viscosupplementation at Week 1 and that the WOMAC (P=0.038) and VAS scores (P=0.014) were lower in the group triamcinolone + viscosupplement in comparison to the group viscosupplement. There were no significant differences in the groups at Weeks 4, 12, and 24.[70]

Ertürk et al.[71] conducted a RCT comparing the clinical effects of combined treatments (IA HA injections combined with a corticosteroid lidocaine) with HA injections alone in patients with symptomatic knee OA. They found that during the first 3 weeks, the combination group had significantly better VAS scores, WOMAC pain subscales, WOMAC total scales, and HSS knee scores than in the group of HA injections only (P<0.01). However, the were no statistically significant differences at Weeks 6, 12, 26, and 52.[71]

Hangody et al.[72] conducted a RCT that evaluated the efficacy and safety of an IA injection of Cingal (a cross-linked sodium hyaluronate combined with triamcinolone hexacetonide) in comparison with Monovisc or saline in the treatment of

knee OA. Cingal provided the immediate and long-term relief of OA-related pain, stiffness, and function when compared to saline (P=0.0099). Cingal also has immediate advantages when compared with Monovisc (P<0.01), but showed similar benefits to Monovisc after 6 weeks.[72]

According to several meta-analyses, IA injections of combined corticosteroid and HA did not exhibit any significant differences in pain control and functional improvement. Some RCTs have reported short-term relief of pain at 4 week and for up to 3 months. However, there were no differences in WOMAC and pain scores after these periods.

We concluded that during the early periods, patients who received a co-treatment of HA and corticosteroid may experience some pain relief with improved knee function faster than those who received HA alone. However, after those periods, the combined use of HA and corticosteroid did not show any added benefits in terms of pain control and knee function.

คำถามที่ 13: การบริหารยาที่ต่างกันของน้ำข้อเทียมมีผลในการรักษาต่างกันหรือไม่

Question 13: Does HA with different injection regimens provide different results?

ความเห็นร่วม: มีหลักฐานไม่เพียงพอ การฉีดน้อยครั้งอาจลดภาวะแทรกซ้อนจากการฉีดยา

Consensus: There is currently not enough evidence. However, having fewer injections may reduce the instances of adverse events.

Delegate vote: Agree: 92.75%, Disagree: 2.9%, Abstain: 4.35% (Strong Consensus)

Justification: Although HA has shown positive clinical outcomes,[51-57] the regimen for injection varies widely, such as being given one injection, three injections, or five injections. One or three injections were recommended for HMWPE and three or five injections were recommended for intermediate MWPE and LMWPE.[54,61] Previous studies have shown that one injection and three injections led to similar VAS scores for pain and WOMAC. More than three injections were associated with a higher VAS score for pain, a lower functional score, and a higher percent of patients requesting to stop the study due to injection site complication, such as redness, pain, and synovitis.[39]

In conclusion, administering one or three injections have similar clinical outcomes. However, more than three injections, and up to five injections, has shown injection site complications with suboptimal clinical outcomes.

คำถามที่ 14: Platelet-rich plasma มีประโยชน์ทางคลินิกในการรักษาข้อเข่าเสื่อมอย่างไร

Question 14: What are the clinical benefits of platelet-rich plasma (PRP) injections in knee OA?

ความเห็นร่วม: ลดอาการปวดใน 12 เดือนแรกหลังการรักษา

Consensus: Patients experience pain relief during the first twelve months.

Delegate vote: Agree: 69.57%, Disagree: 5.8%, Abstain: 24.64% (Strong Consensus)

Justification: Numerous studies have evaluated the effect of platelet-rich plasma (PRP). PRP are highly concentrated growth factors and inflammatory mediators that have been reported to enhance chondrocyte proliferation.

Cole et al.[73] conducted a prospective double-blind randomized controlled trial on 111 patients comparing the efficacy of HA and PRP. He found that VAS scores and International Knee Documentation Committee (IKDC) scores of patients in the PRP group were better than those in the HA group at 24 weeks and for up to 52 weeks. However, in the HA group, VAS scores rose to near pre-injection levels at 52 weeks, which was also statistically significant in the PRP group at 52 weeks.

Lana et al.[74] also conducted a prospective double-blind randomized controlled trial on 105 patients divided into three groups: those receiving IA HA, IA PRP, and combined IA HA and PRP. They found that IA PRP and IA HA+PRP had significantly better VAS scores at 360 days compared to IA HA.

Huang et al.[36] also conducted a prospective randomized controlled study on PRP with 120 patients by comparing IA HA, IA PRP, and IA corticosteroids. The IA PRP group had better VAS scores at 12 months and better WOMAC scores from 6 months to 12 months.

Moreover, Lisi et al.[75] observed, in MRI scans, that IA PRP resulted in increased cartilage thickness in comparison to IA HA. Also, the WOMAC ADL scores and Lequesne scores were better in the IA PRP group than in the IA HA group.

Ahmed et al.[76] conducted a randomized controlled study that compared IA HA and IA PRP in 89 patients by assessing VAS scores and IKDC scores. Moreover, in this study, he also used an ultrasound to determine synovial thickness and a

doppler ultrasound for synovial vascularity. The study found better VAS scores, IKDC scores, and lower synovial hypertrophy and vascularity in the IA PRP group.

However, some research has shown no significant differences between IA PRP and IA HA.[77-81] However, the results presented here on IA PRP do not differ from IA PRP. There fore, it is safe to conclude that, based on current evidences, IA PRP has an effect on pain relief for up to 12 months and may improve function.

คำถามที่ 15: ภาวะแทรกซ้อนจากการฉีด platelet-rich plasma มีอะไรบ้าง

Question 15: What are adverse events associated with PRP injections?

ความเห็นร่วม: การติดเชื้อและปฏิกิริยาอักเสบ

Consensus: Some adverse events include infection and inflammatory reactions.

Delegate vote: Agree: 94.2%, Disagree: 1.45%, Abstain: 4.35% (Strong Consensus)

Justification: In 2016-2018, Huang et al.[82] conducted a prospective randomized controlled study comparing the efficacy of IA HA, IA CS and IA PRP, with 40 knees per group. Several adverse events, including DVT, low-grade fever, infection, and pain, were monitored after the injections. The only adverse event found in all 3 groups was pain after the injection in 2 cases (1.7%), 3 cases (2.5%) and 5 cases (4.2%) in the IA HA, IA CS and IA PRP groups, respectively (p=0.46). No occurrences of DVT, low-grade fever, or infection were found in any of the groups during the 12 months of follow-up.[82]

In 2015, Laudy et al.[83] conducted a meta-analysis that assessed adverse events with the following variables: (1) short-term local and systemic reactions; (2) infections; and (3) withdrawals due to adverse events. However, only short-term local reactions (pain and effusion) and systemic reactions (nausea and dizziness) were observed and reported.[83]

This review was detected in the placebo-controlled study as well as in the comparison with HA studies with no statistically significant differences in the total number of patients with short time local and systemic reactions during and after the injections. (PRP vs saline = 6/27 vs 0/23, p=0.09; PRP vs HA = 20/152 vs 20/150, p=1.00).[84-89]

Controversially, Patel et al.[85] reported higher instances of short-term local and systematic reactions in the two PRP injection groups (single PRP vs saline = 6/27 vs 0/23, p=0.09 ; double PRP vs saline = 11/25 vs 0/23, p=0.03). However, it is obvious that a higher number of injections can be responsible for the higher amount of adverse reactions. However, regarding this particular study, no conclusions were made on the dose-response relationship.

When comparing post-injective pain in IA HA and IA PRP, no statistically significant differences were detected in the number of patients reporting post-injective pain reactions (pooled RR=1.00; 95% CI: 0.65-1.53; p=1.00).[84,88,89] However, Filardo et al.[86] reported a significantly higher post-injective pain reaction in the PRP group (p= 0.039).

In a clinical study by Taniguchi,[90] 22 adverse events were reported during 30 injections in 10 patients. All events were generally mild reactions, and no patients withdrew from the study due to serious adverse events from IA PRP injections. All adverse events, including local pain, itching/tingling

sensation, and stiffness, were resolved spontaneously within 48 hours after the injection. There were no reports of infection or inflammation.

In 2018, Wu et al.[91] conducted an RCT comparing IA PRP with a saline control group that included 40 knees. They found a significant reduction in WOMAC-pain and -total scores in comparison to the normal saline group ($p<0.05$). Neither obvious complications, nor adverse effects related to the injections, were observed during the treatment and follow-up period in both groups.

However, there has been a concerning case report of *Staphylococcus aureus* septic arthritis after an IA injection of autologous PRP in North Carolina in October 2013. Unfortunately, the authors of this abstract chose not to display their results online due to clearance issues.

Current research supports the safety of IA PRP, with a low rate of minor adverse events, e.g., post-injection pain and local inflammation as joint effusion, which recovered after a short period of time. Minor systemic reactions, such as dizziness and nausea, were also reported. Although, rates of complications may increase after repeated injection, there is currently a lack of sufficient evidence to confirm this hypothesis.

Although only a few reports on post-injective infection have been published, the native risks of such procedures presumably exist and should be minimized by all means necessary.[43,92,93] The patient should also be informed of all possible adverse events prior to the procedure, with the physician made aware of the potential for infection and ready to deliver prompt treatment in the face of infections.

คำถามที่ 16: วิธีการเตรียม platelet-rich plasma ที่ต่างกันมีประโยชน์ในการรักษาข้อเข่าเสื่อมต่างกันหรือไม่

Question 16: Do different PRP preparations have different benefits in treating knee OA?

ความเห็นร่วม: ไม่สามารถสรุปได้

Consensus: Current results are inconclusive.

Delegate vote: Agree: 92.65%, Disagree: 2.94%, Abstain: 4.41% (Strong Consensus)

Justification: In current practice, PRP has been separated by the number of leukocytes in the final product of PRP. There are two types of PRP: leukocyte-rich PRP (LR-PRP) and leukocyte-poor PRP (LP-PRP). The LR-PRP contain high concentrations of leukocytes, which also contain high concentration of TNF-α, IL-1β, IL-6, interferon-γ.[94-96] However, LP-PRP does not contain any of these inflammatory mediators. Moreover, LP-PRP has a high concentration of anti-inflammatory mediators IL-4 and IL-10. IL-10 may also suppress the release of inflammatory mediators, such as TNF-α, IL-6, and IL-1β, and block the inflammatory pathway.[94,95,97,98] Several randomized controlled studies found that LP-PRP is better than HA in providing pain relief.[73,82,99] However, Joshi et al. [80] conducted a randomized controlled study on LP-PRP and failed to demonstrate the superiority of LP-PRP in comparison to corticosteroids in severe knee OA. For a study on LR-PRP, Lana[74] included 105 patients divided into 3 groups: IA HA, IA LR-PRP, and IA LR-PRP+HA. The study found that LR-PRP is superior to HA, with better VAS scores at 1, 3, 6, and 12 months. LR-PRP WOMAC physical activity scales were also better than HA at

12 months. However, other LR-PRP studies failed to demonstrate its superior efficacy in comparison to HA.[77,78,100] An additional confounding factor is that each study has a different method of preparation for LP-PRP and LR-PRP.[73,74,77,78,80,82,99,100] In conclusion, LP-PRP may have better results than LR-PRP, but the method of preparation for each LP-PRP varies between studies. Therefore, more data is needed to confirm its superior efficacy over LP-PRP. Moreover, it is difficult to conclude which method of preparing LP-PRP is better.

คำถามที่ 17: Platelet-rich plasma สามารถชะลอการทำลายกระดูกอ่อนผิวข้อในข้อเข่าเสื่อมได้หรือไม่

Question 17: Can PRP delay cartilage destruction/degradation in knee OA?

ความเห็นร่วม: ไม่สามารถสรุปได้ เนื่องจากมีหลักฐานอย่างจำกัด

Consensus: Results are currently inconclusive due to limited evidence.

Delegate vote: Agree: 94.2%, Disagree: 0%, Abstain: 5.8% (Strong Consensus)

Justification: Xie et al.[101] conducted a study that shows the benefits of PRP in an arthritis model. The results suggest that PRP has an inhibitory effect on traumatic OA progression and that PRP-injected knee samples show a significant reduction in macroscopic and histologic cartilage degeneration scores compared to controls. Another study from Annaniemi et al.[102] report benefits of PRP in terms of prolonging the time until total knee arthroplasty surgery compared to HA injections; however, no direct evidence for delaying cartilage destruction was observed.

However, there is currently no well-designed study that shows the advantages of PRP injections in delaying cartilage degradation. Therefore, we cannot conclude any benefits of PRP in terms of delaying cartilage destruction/degradation in knee OA due to the limited amount of evidence.

คำถามที่ 18: Platelet-rich plasma สามารถฟื้นฟูกระดูกอ่อนผิวข้อในข้อเข่าเสื่อมขึ้นมาใหม่ได้หรือไม่

Question 18: Can PRP promote cartilage regeneration in knee OA?

ความเห็นร่วม: มีหลักฐานไม่เพียงพอ

Consensus: There is currently not enough evidence.

Delegate vote: Agree: 94.2%, Disagree: 1.45%, Abstain: 4.35% (Strong Consensus)

Justification: There are at least 3 studies that show the enhancing effects of PRP on chondrocyte proliferation. Smyth et al.[103] retrospectively reviewed 21 studies (12 studies *in vitro*, 8 *in vivo*, and 1 that was both in vitro and in vivo), which found that PRP can increase chondrocytes and mesenchymal stem cell proliferation. Xie et al.[101] summarized that PRP may have the potential to fill cartilage defects and enhance cartilage repair. A systematic review by Fortier et al.[104] shows the possibility of chondrocyte proliferation after PRP exposure, but with varying results.

Currently, there is still a lack of well-designed studies showing that PRP can promote cartilage regeneration in knee OA. Therefore, we cannot conclude that PRP promotes cartilage regeneration in knee OA due to the limited amount of evidence, with additional studies still needed.

คำถามที่ 19: ยาแก้ปวดประเภทใช้ภายนอกชนิดใดบ้างมีประโยชน์ในการลดปวดจากข้อเข่าเสื่อม

Question 19: Which topical analgesics would be beneficial for pain relief in knee OA?

ความเห็นร่วม: ยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์ และแคปไซซิน

Consensus: Topical NSAIDs, Capsaicin

Delegate vote: Agree: 97.1%, Disagree: 1.45%, Abstain: 1.45% (Strong Consensus)

Justification: A meta-analysis reviewing topical NSAIDs for the treatment of chronic musculoskeletal pain (lasting more than 3 months) showed them to be effective in treating painful knee arthritis. Diclofenac and ketoprofen are two drugs that were found to be of good quality and with a long duration of study. The number of treatments needed to be clinically successful was 9.8 for topical diclofenac (95% CI: 7.1-16) and 6.9 for topical ketoprofen (95% CI: 5.4-9.3) when compared to carriers or other active treatments.[105]

A cross-over, double-blind, randomized, controlled trial of 100 patients comparing 0.0125% capsaicin with a placebo found significantly better VAS scores and WOMAC scores in the capsaicin group.[106] Five double-blind, randomized, controlled trials, and one crossover trial found capsaicin to be moderately effective in reducing pain intensity in comparison to a placebo.[107]

There is currently no adequate English language literature on the efficacy of herbal remedies which include plaivana cream and longanoid cream, for the treatment of chronic pain in knee OA.

คำถามที่ 20: ภาวะแทรกซ้อนของยาแก้ปวดชนิดใช้ภายนอกสำหรับข้อเข่าเสื่อมมีอะไรบ้าง

Question 20: What are adverse events related to topical analgesics in knee OA?

ความเห็นร่วม: ปฏิกริยาอักเสบบริเวณผิวหนัง

Consensus: Skin reactions

Delegate vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous Consensus)

Justification: Points of concern regarding topical analgesics are local adverse events, such as skin irritations, redness, erythema, itching, or pruritis. Based on their topical application, topical analgesics may have similar rates of skin reactions as placebos and oral medications for patients with OA. Past research has shown that topical analgesics can cause skin reactions. A study by Barthel found higher rates of adverse skin events for topical NSAIDs than placebos in patients with OA.

According to Cochrane reviews, Derry et al.[105] found that topical analgesics, specifically topical diclofenac and topical salicylates, can cause adverse skin reactions. Capsaicin, a topical analgesic with strong evidence-based data for OA treatment, also causes local burning sensations. Kosuwan et al.[106] performed a double-blind randomized controlled trial regarding topical capsaicin in treating OA. This study found that 67% of patients using topical capsaicin experienced a burning sensation. However, none of the patients withdrew from the study based due to burning sensations. A review study by Laslett et al.[4] also found a burning effect from a mild topical capsaicin application in 35 to 100% of participants.

In this consensus meeting, experts also strongly agree that skin reactions are an adverse event of topical analgesics in knee OA that should be considered during treatment.

คำถามที่ 21: ยาแก้ปวดชนิดใช้ภายนอกเป็นสาเหตุให้เกิดภาวะแทรกซ้อนของระบบอื่นๆในร่างกาย (systemic adverse effects) ได้หรือไม่

Question 21: Do topical analgesics cause any systemic adverse effects?

ความเห็นร่วม: ไม่ได้

Consensus: No

Delegate vote: Agree: 94.2%, Disagree: 4.35%, Abstain: 1.45% (Strong Consensus)

Justification: Blood drug levels from topical NSAIDs are much lower than oral NSAIDs. The plasma concentration of topical NSAIDs is usually less than 5% of the plasma concentration found in oral NSAIDs administration. The most common adverse reaction of topical NSAIDs is skin irritation. Systemic adverse events, including headache, dyspepsia, diarrhea, and drowsiness, were no different between topical NSAIDs and a carrier (topical placebo). The adverse gastrointestinal events were also similar between topical diclofenac (n=3,240 participants; RR=1.1; 95% CI: 0.76-1.6) and topical ketoprofen (n=2,621 participants; RR=0.96; 95% CI: 0.69-1.3).[105] A study on the use of diclofenac sodium gel did not find any meaningful differences in adverse events related to liver or kidney function when compared to a placebo.[108] Compared with oral NSAIDs, topical NSAIDs have lower gastrointestinal complications.[105,109]

คำถามที่ 22: ยาแก้ปวดชนิดใช้ภายนอกปลอดภัยกว่ายาชนิดรับประทานสำหรับข้อเข่าเสื่อมหรือไม่

Question 22: Are topical analgesics safer than oral medications in the treatment of knee OA?

ความเห็นร่วม: ปลอดภัยกว่า

Consensus: Yes

Delegate vote: Agree: 98.55%, Disagree: 0%, Abstain: 1.45% (Strong Consensus)

Justification: Oral medications are a common non-surgical treatment for patients with OA. However, there are many systemic effects from oral medications, especially NSAIDs, including concerns regarding cardiovascular, gastrointestinal, and renal systems. Topical analgesics are an alternative option for the non-surgical treatment of OA to avoid the systemic effects caused by oral medications, with several evidence-based studies showing that topical analgesics cause less systemic adverse events.[105] Derry et al. reviewed topical NSAIDs for chronic musculoskeletal pain and found fewer systemic adverse events caused by topical NSAIDs when compared with oral NSAIDs (17% vs 26%, respectively). They concluded that topical NSAIDs have very low occurrences of adverse events that have harmful systemic effects.[105] In this consensus meeting, experts also strongly agree that topical analgesics are safer than oral medications in OA treatment.

คำถามที่ 23: การรักษาใดเหมาะสมเป็นลำดับแรกในผู้ป่วยข้อเข่าเสื่อมที่มีภาวะข้ออักเสบเฉียบพลันระหว่าง น้ำข้อเทียม ยาฉีดสเตียรอยด์เข้าข้อ และ platelet-rich plasma

Question 23: Which of the following should be used first when treating acute inflammatory knee OA: HA, steroids, or PRP?

ความเห็นร่วม: ยาฉีดสเตียรอยด์เหมาะสมในการรักษาผู้ป่วยข้อเข่าเสื่อมที่มีภาวะข้ออักเสบเฉียบพลันเป็นลำดับแรกเพื่อลดอาการปวดในระยะสั้น

Consensus: Steroids should be used first to reduce pain for a quick and short-term period.

Delegate vote: Agree: 91.3%, Disagree: 7.25%, Abstain: 1.45% (Strong Consensus)

Justification: Steroids decrease inflammation and reduce the activity of the immune system.[1] A high quality meta-analysis on corticosteroid injections for knee OA revealed the RR on improvements for up to 2 weeks post-injection, which was 1.66 (95% CI: 1.37-2.0), with the amount of injections needed to show improvements at 1.3 to 3.5 per patient patients.[110] Steroid treatments resulted in short-term (up to two weeks) and rapid improvements in pain, with significant improvements also shown over a longer term (16-24 weeks). Moreover, a recent network meta-analysis of 129 trials (n=32,129 patients) on the pharmacologic treatment of knee OA revealed that IA corticosteroids have higher efficacy than IA placebos and all other oral treatments.[4]

In 2014, Egemen et al.[111] reviewed IA injections for treating knee OA by comparing IA corticosteroid, HA, and PRP injections. They found that IA corticosteroid injections could

be considered as an adjunct therapy to core treatments in the short-term reduction of moderate to severe pain. IA HA injections were found to have high efficacy, with pain reduction in mild knee OA for up to 24 weeks. However, whether HA injections are cost-effective is an important concern that patients should be made aware of. Although more high-quality evidence is still needed, recent studies showed that IA PRP injections can relieve pain and improve knee function and quality of life, especially in younger patients, and in mild OA cases.

คำถามที่ 24: การรักษาใดเหมาะสมเป็นลำดับแรกในผู้ป่วยข้อเข่าเสื่อมที่ไม่มีภาวะน้ำในข้อมากจากการอักเสบเฉียบพลัน (knee effusion) ระหว่างน้ำข้อเทียม ยาฉีดสเตียรอยด์เข้าข้อ และ platelet-rich plasma

Question 24: Which treatment should be used first in treating knee OA without effusion: HA, steroid, or PRP?

ความเห็นร่วม: ไม่สามารถสรุปได้

Consensus: Inconclusive

Delegate vote: Agree: 84.06%, Disagree: 13.04%, Abstain: 2.9% (Strong Consensus)

Justification: Currently, the results are inconclusive as there is currently no strong evidence within the current literature that suggests whether HA, steroids, or PRP should be used first in treating knee OA without effusion. However, many comparative studies have summarized results on HA, steroid, and PRP in treating knee OA.

In a Cochrane review of trials comparing IA HA injections with IA corticosteroids, there were no significant differences found at 4 weeks post-injection; however, IA HA was shown to be more effective between 5 and 13 weeks post-

injection.[48,112] This is further supported by a meta-analysis of seven RCTs in patients with knee OA in which IA HA was compared directly with IA corticosteriods.[65] In the first two weeks, IA corticosteroids injections were more effective in relieving pain, but at Week 4, both HA and corticosteroids were equally effective, and from Week 8, HA was more effective until the last assessment at Week 26. Analyses on other outcomes, such as reduction in stiffness and improvement in function, following IA HA and corticosteroids injections were similar.

In recent studies comparing PRP and HA, Kon et al.[113] compared PRP against HA injections in 150 patients, with PRP treatments resulting in better outcomes than HA in reducing pain and symptoms and in recovering articular function for up to 6 months. In this study, PRP was more effective than HA in younger patients affected by cartilage lesions or early OA. However, PRP and HA treatments offered similar results in patients over 50 years of age and in the treatment of advanced OA. Additionally, Spakova et al.[114] compared 120 patients receiving either IA HA or IA PRP. The authors found that patients who received PRP injections after a 3- and 6-month follow-up period had significantly better outcomes. Say et al.,[115] compared IA HA and IA PRP injections in a prospective study and concluded that the application of a single dose of PRP was a safe, effective, and low-cost method for treating OA. Finally, three recent Level 1 studies, two randomized HA controlled clinical trials[87,88] and one placebo-controlled trial,[85] found that PRP decreased pain and improved function in all three trials when compared to HA or a placebo.

We conclude that IA corticosteroids injections can be used as an adjunct treatment to core treatments in the short-term reduction of moderate-to-severe pain in people with

OA. IA HA injections may exhibit high efficacy and provide pain reduction in mild knee OA for up to 24 weeks. However, the cost-effectiveness of IA HA is an important concern that patients should be informed of. Although more high-quality evidence is still needed, recent studies show that PRP injections are promising in relieving pain and improving knee function and quality of life, especially in younger patients and those with mild OA.

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