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และวารสารเวชศาสตร์เขตเมือง

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คำชี้แจงการส่งบทความ

วชิรเวชสารเป็นวารสารการแพทย์ของคณะแพทยศาสตร์-วชิรพยาบาล มหาวิทยาลัยนวมินทราธิราช เริ่มพิมพ์ครั้งแรกในปีพ.ศ. 2500 และพิมพ์เผยแพร่อย่างสม่ำเสมอ ปีละ 6 ฉบับ ทุก 2 เดือน (มกราคม-กุมภาพันธ์, มีนาคม-เมษายน, พฤษภาคม-มิถุนายน, กรกฎาคม-สิงหาคม, กันยายน-ตุลาคม และพฤศจิกายน-ธันวาคม) และมีฉบับเพิ่มเติมปีละ 1 เล่ม เพื่อตีพิมพ์ผลงานที่นำเสนอในงานประชุมวิชาการของมหาวิทยาลัยหรือของคณะ โดยมีวัตถุประสงค์เพื่อเผยแพร่ผลงานวิจัยในรูปแบบของนิพนธ์ต้นฉบับ รายงานผู้ป่วยและบทความวิชาการทางการแพทย์ รวมทั้งผลงานวิชาการด้านแพทยศาสตรศึกษาและวิทยาศาสตร์สุขภาพ

วชิรเวชสารมุ่งเน้นความรู้เกี่ยวกับเวชศาสตร์เขตเมือง ได้แก่ วิทยาศาสตร์พื้นฐานและวิทยาศาสตร์การแพทย์คลินิก รวมถึง ระบาดวิทยา สมุฏฐานวิทยา พยาธิกำเนิด การวินิจฉัย และการดูแลรักษาโรคอันเกี่ยวข้องกับสุขภาพของประชาชนในเขตเมือง

บทความที่ส่งมาตีพิมพ์จะได้รับการกลั่นกรองโดยผู้ทรงคุณวุฒิที่มีความเชี่ยวชาญในสาขานั้น ๆ อย่างน้อย 2 ท่านในแง่ของความเหมาะสมทางจริยธรรม วิธีการดำเนินการวิจัย ความถูกต้อง ความชัดเจนของการบรรยายในการนำเสนอ รายชื่อของผู้นิพนธ์และผู้กลั่นกรองจะได้รับการปกปิด โดยกองบรรณาธิการก่อนส่งเอกสารไปให้ผู้เกี่ยวข้องทั้ง 2 ฝ่าย กองบรรณาธิการขอสงวนสิทธิ์ในการตรวจแก้ไขบทความก่อนพิจารณาตีพิมพ์ ทั้งนี้ข้อความและความคิดเห็นในบทความนั้น ๆ เป็นของเจ้าของบทความโดยตรง

บทความที่ส่งมาต้องไม่เคยพิมพ์ที่ใดมาก่อน และไม่อยู่ระหว่างการพิจารณาเพื่อพิมพ์ที่ใด ๆ ยกเว้นในรูปแบบบทคัดย่อหรือเอกสารบรรยาย กรณีที่บทความได้รับการพิมพ์ในวชิรเวชสารแล้ว ผู้นิพนธ์จะได้รับสำเนาพิมพ์ 30 ฉบับ ภายหลังหนังสือเผยแพร่เรียบร้อยแล้ว และผู้นิพนธ์ไม่สามารถนำบทความดังกล่าวไปนำเสนอหรือพิมพ์ในรูปแบบใด ๆ ที่อื่นได้ ถ้าไม่ได้รับคำอนุญาตจากวชิรเวชสาร

หลักเกณฑ์ทั่วไปในการเตรียมและส่งต้นฉบับ

การส่งต้นฉบับ ให้ส่ง 3 ชุด พร้อม diskette หรือแผ่น CD หรือส่ง ทางระบบ online (https://tci-thaijo.org/index.php/VMED และ http://thailand.digitaljournals.org/index.php/VMJ/) หรือส่ง ทางระบบ online (https://tci-thaijo.org/index.php/VMED และ http://thailand.digitaljournals.org/index.php/VMJ/) พร้อมรายการตรวจสอบบทความ และจดหมายเพื่อขอพิมพ์ ไปยังกองบรรณาธิการ ซึ่งจดหมายนี้ต้องมีชื่อ ที่อยู่ หมายเลขโทรศัพท์ โทรสาร และ email address ของผู้นิพนธ์ ระบุว่า ผู้นิพนธ์ท่านใดเป็นผู้รับผิดชอบหลัก และต้นฉบับนั้นเป็นบทความประเภทใด (นิพนธ์ต้นฉบับ รายงานผู้ป่วย หรือบทความวิชาการ) รวมทั้งต้องมีข้อความว่าผู้นิพนธ์ทุกท่านได้อ่านและเห็นด้วยกับต้นฉบับนั้น และเชื่อว่าต้นฉบับนั้นรายงานผลตรงตามผลการวิจัยที่ได้ศึกษา และต้นฉบับนั้นไม่เคยพิมพ์ที่ใดมาก่อนและไม่อยู่ระหว่างการพิจารณาเพื่อพิมพ์ที่ใด ๆ ในกรณีที่เรื่องนั้นเคยพิมพ์ในรูปบทคัดย่อ หรือวิทยานิพนธ์ หรือเคยนำเสนอในที่ประชุมวิชาการใด ๆ จะต้องแจ้งให้กองบรรณาธิการทราบด้วย สำหรับเรื่องที่ทำการศึกษาในคน จะต้องมีหนังสืออนุญาตจากคณะกรรมการจริยธรรมการศึกษาวิจัยในมนุษย์แนบมาด้วย

ต้นฉบับจะเป็นภาษาไทยหรือภาษาอังกฤษก็ได้ ถ้าเป็นภาษาไทยควรใช้ภาษาไทยให้มากที่สุด ยกเว้นคำภาษาอังกฤษที่ไม่มีคำศัพท์นั้น ๆ ในภาษาไทยหรือแปลแล้วได้ใจความไม่ชัดเจน ภาษาอังกฤษที่ใช้ให้ใช้ตัวพิมพ์เล็กทั้งหมดยกเว้นชื่อเฉพาะที่ให้ใช้ ตัวพิมพ์ใหญ่เฉพาะอักษรต้น ตัวเลขใช้เลขอารบิก เนื้อหาควรมีความกระชับโดยมีความยาวเหมาะสมกับการพิมพ์ การพิมพ์ต้นฉบับให้ใช้ font Cordial New 16 พิมพ์หน้าเดียวบนกระดาษ A4 และพิมพ์บรรทัดเว้นบรรทัด โดยเว้นระยะห่างจากขอบทั้ง 4 ด้านไม่น้อยกว่า 1 นิ้ว โดยไม่ต้องปรับขอบด้านขวาให้ตรงกัน

รายการตรวจสอบบทความ (checklist guideline)

ผู้นิพนธ์ต้องตรวจสอบต้นฉบับที่จัดเตรียมให้ครบถ้วนถูกต้องตรงตามรายการตรวจสอบบทความ และส่งมาพร้อมกับบทความ บทความที่ส่งมาโดยไม่มีใบรายการตรวจสอบบทความ หรือมีไม่ครบหรือไม่ถูกต้องตามที่กำหนดไว้จะถูกส่งกลับก่อนการดำเนินการใด ๆ ทั้งสิ้น ผู้นิพนธ์สามารถ download รายการตรวจสอบบทความชนิดต่าง ๆ ได้จาก website ของวชิรเวชสาร (http://www.vajira.ac.th/vmj)

คำแนะนำในการเขียนบทความ

การวิจัยแบบสุ่ม การวิจัยเพื่อการวินิจฉัยโรค และการวิจัยเชิงสังเกต ควรจะตรวจสอบความถูกต้องครบถ้วนของเกณฑ์ตามแนวทางของ Consort 2010 checklist, STARD checklist และ STROBE checklist ตามลำดับ ผู้นิพนธ์สามารถอ่านรายละเอียดเพิ่มเติมได้ผ่านทาง website ของวชิรเวชสาร

ผู้นิพนธ์ควรเตรียมบทความตามแนวทางการเขียนบทความทางวิทยาศาสตร์สุขภาพของคณะบรรณาธิการวารสารนานาชาติ (International Committee of Medical Journal Editors) ซึ่งมีรายละเอียดทาง website http://www.icmje.org/recommendations/ ดังจะสรุปไว้เป็นแนวทางดังต่อไปนี้ คือ บทความที่ส่งเพื่อพิจารณาตีพิมพ์ ควรเขียนเรียงตามลำดับ ดังนี้ ชื่อเรื่องและผู้นิพนธ์ บทคัดย่อ เนื้อหาหลัก กิตติกรรมประกาศ เอกสารอ้างอิง

1. ชื่อเรื่อง (title) ควรตั้งชื่อเรื่องให้กะทัดรัด ได้ใจความชัดเจน ไม่ใช้ตัวย่อใด ๆ ชื่อเรื่องภาษาไทยให้ใช้ภาษาไทยทั้งหมด ภาษาอังกฤษที่มีในชื่อเรื่องให้แปลเป็นไทย ถ้าแปลไม่ได้ให้เขียนทับศัพท์ ถ้าเขียนทับศัพท์ไม่ได้ ให้เขียนเป็นภาษาอังกฤษด้วยตัวพิมพ์เล็กยกเว้นชื่อเฉพาะที่ให้ใช้ตัวพิมพ์ใหญ่เฉพาะอักษรต้น ชื่อเรื่องภาษาอังกฤษให้ใช้ตัวพิมพ์ใหญ่ในอักษรต้นตัวแรกของทุกคำ ยกเว้นคำบุพบท

2. ผู้นิพนธ์ (authors) เขียนชื่อ นามสกุล และคุณวุฒิของผู้นิพนธ์ คุณวุฒิภาษาไทย เขียนด้วยตัวย่อตามพจนานุกรม เช่น พ.บ. ว.ว.ศัลยศาสตร์ หรือ วท.บ. กศ.บ. คุณวุฒิภาษาอังกฤษ ให้เขียนตัวย่อโดยไม่ต้องมีจุด เช่น MD, PhD, FICS, FRCST, MRCOG เป็นต้น หลังคุณวุฒิให้ใส่เครื่องหมายเชิงอรรถ (footnotes) กำกับให้รายละเอียดสถานที่ทำงานในบรรทัดล่างของหน้าแรก เชิงอรรถใช้ตัวเลขเรียงจากเลข 1 ขึ้นไป และให้ใส่เครื่องหมายดอกจันหลังคุณวุฒิของชื่อผู้ติดต่อ หรือ corresponding author และให้ e-mail address ของผู้ติดต่อในบรรทัดล่างสุดของหน้าแรกต่อจากรายละเอียดสถานที่ทำงานของผู้นิพนธ์และผู้นิพนธ์ร่วม

3. บทคัดย่อ (abstract) หมายถึง เรื่องย่อของงานวิจัย ซึ่งต้องมีทั้งภาษาไทยและภาษาอังกฤษ เนื้อหาต้องมีความสมบูรณ์ในตัวเอง โดยเขียนให้สั้นที่สุดและได้ใจความ บทคัดย่อทั้งภาษาไทยและภาษาอังกฤษต้องมีเนื้อหาเหมือนกัน ไม่ใส่ตารางหรือแผนภูมิใด ๆ ไม่มีการอ้างอิงเอกสาร ไม่ใส่ตัวเลขหรือข้อความที่ไม่ปรากฏในผลการวิจัย สำหรับบทคัดย่อภาษาอังกฤษให้ใช้ past tense เท่านั้น และให้ใส่ keywords ต่อท้าย ไม่เกิน 3-5 คำหรือวลี เพื่อใช้เป็นดัชนี

นิพนธ์ต้นฉบับให้เขียนบทคัดย่อแบบ structured abstract ส่วนรายงานผู้ป่วยและบทความวิชาการให้เขียนบทคัดย่อแบบปกติย่อหน้าเดียว (standard abstract) ซึ่งควรมีจำนวนคำทั้งหมดไม่เกิน 300 คำ structured abstract ให้เขียน 4 หัวข้อหลัก ซึ่งประกอบด้วย วัตถุประสงค์ (objective) วิธีดำเนินการวิจัย (methods) ผลการวิจัย (results) และสรุป (conclusion) โดยวัตถุประสงค์ควรกล่าวถึงจุดมุ่งหมายหลัก

ที่ต้องการศึกษาหรือทฤษฎีที่ต้องการทดสอบ วิธีดำเนินการวิจัยควรรวมถึงรูปแบบการทำวิจัย สถานที่ทำการวิจัย จำนวนและลักษณะของกลุ่มตัวอย่าง วิธีการรักษาหรือทดลอง ผลการวิจัยหมายถึงผลลัพธ์ส่วนที่สำคัญที่สุดของการศึกษา และสรุปควรเน้นถึงความสำคัญของผลการวิจัย

4. เนื้อหาหลัก ในส่วนของนิพนธ์ต้นฉบับ ควรประกอบด้วย 4 หัวข้อหลัก ได้แก่ บทนำ วิธีดำเนินการวิจัย ผลการวิจัย และวิจารณ์ รายงานผู้ป่วย ควรมี 4 หัวข้อหลัก คือ บทนำ รายงานผู้ป่วย วิจารณ์และสรุป ส่วนบทความวิชาการ ให้ปรับหัวข้อหลักตามความเหมาะสมกับบทความนั้น ๆ

บทนำ ควรกล่าวถึงความเป็นมาของปัญหา เช่น ลักษณะและความสำคัญของปัญหาที่จะนำมาศึกษา มีการเน้นถึงความรู้เดิมของปัญหาโดยอ้างอิงจากเอกสารที่เกี่ยวข้องตามสมควรเพื่อนำผู้อ่านเข้าสู่เรื่องที่จะทำวิจัย รวมทั้งบอกวัตถุประสงค์ในการทำวิจัยอย่างชัดเจน ทั้งนี้บทนำไม่ควรยาวเกินไป ไม่ใส่ข้อมูลผลการวิจัย ตารางหรือแผนภูมิใด ๆ และต้องไม่วิจารณ์หรือสรุปในบทนำ

วิธีดำเนินการวิจัย ควรบอกว่าเป็นรูปแบบการวิจัยชนิดใด กลุ่มตัวอย่างขนาดเท่าใด โดยแสดงวิธีคำนวณขนาดตัวอย่างอย่างสั้น ๆ สุ่มตัวอย่างโดยวิธีใด บอกสถานที่ที่ทำการวิจัย ระยะเวลาที่ศึกษา เกณฑ์การคัดเข้าและเกณฑ์การคัดออก บอกรายละเอียดของการวิจัยว่าดำเนินการอย่างไร เพื่อให้ผู้อื่นสามารถนำไปศึกษาซ้ำได้ หากเป็นวิธีที่ใช้อยู่ทั่วไปอาจบอกเพียงชื่อวิธีการพร้อมเอกสารอ้างอิง แต่ถ้าเป็นวิธีใหม่ ต้องแจงรายละเอียดให้ผู้อ่านเข้าใจ รวมทั้งบอกรายละเอียดของการวิเคราะห์ข้อมูลทางสถิติ ว่าใช้โปรแกรมคอมพิวเตอร์อะไรในการวิเคราะห์ข้อมูล ใช้สถิติอะไร และกำหนดระดับนัยสำคัญเท่าใด

ผลการวิจัย ควรนำเสนอให้เข้าใจง่ายและชัดเจน โดยใช้ตารางและแผนภูมิหรือรูปประกอบ แต่ไม่ใช้ตารางและแผนภูมิในเรื่องเดียวกันควรออกแบบให้มีจำนวนตารางและแผนภูมิน้อยที่สุด โดยไม่ควรเกิน 5-7 ตาราง ตารางและแผนภูมิต้องมีเลขที่ และชื่อกำกับ และมีคำอธิบายโดยสรุป เส้นของตารางให้มีเฉพาะเส้นแนวขวาง 3 เส้นที่ด้านบนสุด ด้านล่างสุดของตาราง และเส้นแบ่งหัวข้อตารางกับเนื้อหาเท่านั้น รูปประกอบควรเป็นรูปที่จัดทำขึ้นเอง ถ้าเป็นรูปจากแหล่งอื่นจะต้องระบุที่มา รวมทั้งเอกสารสำเนาลิขสิทธิ์จากสำนักพิมพ์ต้นฉบับด้วย สำหรับรูปผู้ป่วยจะต้องไม่ให้ทราบว่าเป็นบุคคลใดโดยได้รับการปกปิดส่วนที่สามารถระบุถึงบุคคลได้ และอาจจะต้องมีคำยินยอมจากผู้ป่วยด้วย

วิจารณ์ ให้วิจารณ์ผลการวิจัยทั้งหมดที่นำเสนอ สรุปผลการวิจัยสั้น ๆ โดยไม่ต้องลอกข้อความที่เขียนแล้วในผลการวิจัย เปรียบเทียบผลการวิจัยกับการศึกษาอื่น ๆ ให้ความเห็นว่าเหตุใดผลการวิจัยจึงเป็นเช่นนั้น ควรวิจารณ์ข้อจำกัดของการทำวิจัย วิธีดำเนินการวิจัยและความน่าเชื่อถือทางสถิติ รวมทั้งประโยชน์ที่จะนำไปใช้ได้ และการวิจัยที่ควรศึกษาต่อเนื่องต่อไปในอนาคต

5. **Conflict of interest** ให้ระบุว่าผู้นิพนธ์แต่ละท่านมี conflict of interest ใด ๆ หรือไม่ ในจดหมายเพื่อขอพิมพ์

6. **กิตติกรรมประกาศ** แสดงความขอบคุณผู้สนับสนุนการทำวิจัย เช่น ผู้ให้การสนับสนุนทางด้านเทคนิค เครื่องมือที่ใช้ และทางการเงิน นอกจากนี้ควรขอบคุณหน่วยงานหรือผู้รับผิดชอบข้อมูล และผู้ให้คำแนะนำด้านต่าง ๆ

7. **เอกสารอ้างอิง** ให้ใส่หมายเลข 1,2,3 ไว้ท้ายประโยคโดยพิมพ์ตัวยกสูงโดยไม่ต้องใส่วงเล็บ เอกสารที่อ้างอิงเป็นอันดับแรกให้จัดเป็นหมายเลข 1 และเรียงลำดับก่อนหลังต่อ ๆ ไป หากไม่มีความจำเป็นไม่ควรอ้างอิง abstract, unpublished paper, in press หรือ personal communication นิพนธ์ต้นฉบับควรมีเอกสารอ้างอิงไม่เกิน 30 รายการ และไม่ควรใช้เอกสารอ้างอิงที่เก่าเกินไป เอกสารอ้างอิงทั้งหมด รวมทั้งเอกสารอ้างอิงภาษาไทย ให้เขียนเป็นภาษาอังกฤษ โดยเขียนตาม Vancouver guideline ซึ่งกำหนดโดย International Committee of Medical Journal Editors โดยมีหลักโดยย่อดังนี้

ชื่อผู้เขียน ให้ใช้ชื่อสกุลตามด้วย อักษรแรกของชื่อต้นและชื่อกลางเป็นตัวพิมพ์ใหญ่ ใส่ชื่อผู้เขียนทุกคนคั่นด้วยเครื่องหมายจุลภาค ถ้าเกิน 6 คน ใส่ชื่อ 6 คนแรก ตามด้วย et al

การอ้างอิงวารสาร ให้ใส่ชื่อผู้เขียน. ชื่อเรื่อง. ชื่อย่อวารสารตาม index medicus. ปี ค.ศ.; ปีที่ (volume): หน้าแรกถึงหน้าสุดท้าย. โดยเลขหน้าที่ซ้ำกันไม่ต้องเขียน เช่นหน้า 124 ถึงหน้า 128 ให้เขียน 124-8.

ตัวอย่าง: Tangjitgamol S, Hanprasertpong J, Manusirivithaya S, Wootipoom V, Thavaramara T, Buhachat R. Malignant ovarian germ cell tumors: clinico-pathological presentation and survival outcomes. Acta Obstet Gynecol Scand. 2010; 89: 182-9.

การอ้างอิงหนังสือตำรา ให้เขียน ชื่อผู้เขียน. ชื่อหนังสือ. ครั้งที่พิมพ์ (ถ้าพิมพ์ครั้งแรกไม่ต้องเขียน). ชื่อเมือง (ใช้ชื่อเมืองแรกชื่อเดียว): ชื่อโรงพิมพ์; ค.ศ. p.หน้าแรกถึงหน้าสุดท้าย.

ตัวอย่าง: Straus SE, Richardson WS, Glasziou P, Haynes RB. Evidence based medicine: how to practice and teach EBM. 3rd ed. Edinburgh: Churchill Livingstone; 2005. p.10-5.

การอ้างอิงบทหนึ่งในหนังสือตำรา ให้เขียน ชื่อผู้เขียน. ชื่อเรื่อง. In: ชื่อบรรณาธิการ, editor(s). ชื่อหนังสือ. ครั้งที่พิมพ์ (ถ้าพิมพ์ครั้งแรกไม่ต้องเขียน). ชื่อเมือง: ชื่อโรงพิมพ์; ปี ค.ศ. p. หน้าแรก-หน้าสุดท้าย.

ตัวอย่าง: Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p.93-113.

การอ้างอิงบทคัดย่อจากที่ประชุมวิชาการ (published proceedings paper)

ตัวอย่าง: Berger H, Klemm M. Clinical signs of gastric ulcers and its relation to incidence [abstract]. In: Chuit P, Kuffer A, Montavon S, editors. 8th Congress on Equine Medicine and Surgery; 2003 Dec 16-18; Geneva, Switzerland. Ithaca (NY): International Veterinary Information Service (IVIS); 2003. p. 45.

การอ้างอิงจากวารสาร/ข้อมูลทางอิเล็กทรอนิกส์:

ตัวอย่าง: International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals [Internet]. 2014 [updated 2014 Dec 1; cited 2015 Jan 30] Available from: http://www.icmje.org/icmje-recommendations.pdf.

การอ้างอิงจากวิทยานิพนธ์

ตัวอย่าง: Liu-Ambrose TY. Studies of fall risk and bone morphology in older women with low bone mass [dissertation]. [Vancouver (BC)]: University of British Columbia; 2004. 290 p.

การแก้ไขบทความเพื่อส่งตีพิมพ์

ให้ผู้นิพนธ์แก้ไขบทความ และอธิบายชี้แจงข้อสงสัยตามที่ผู้กลั่นกรอง และกองบรรณาธิการให้ข้อเสนอแนะให้ครบทุกประเด็น และควรเน้นหรือขีดเส้นใต้ส่วนที่ได้แก้ไขในบทความพร้อมทั้งมีจดหมายสั้น ๆ ระบุว่าได้แก้ในประเด็นใดบ้าง รวมทั้งอธิบายประเด็นที่ไม่ได้แก้ไขให้ผู้นิพนธ์ส่งคืนบทความที่แก้ไขแล้ว พร้อมทั้งบทความเดิมที่ได้รับจากกองบรรณาธิการ ภายใน 4 สัปดาห์หลังได้รับบทความ ถ้าภายใน 12 สัปดาห์ผู้นิพนธ์ไม่ส่งบทความคืน หรือไม่ได้แก้ไขบทความตามคำแนะนำ ทางกองบรรณาธิการขอสงวนสิทธิ์ในการถอนบทความออกจากการพิจารณาบทความเพื่อตีพิมพ์

Instructions for Authors

Vajira Medical Journal (Vajira Med J) is the official medical journal of the Faculty of Medicine Vajira Hospital, Navamindradhiraj University. The journal was established in 1957 and, since then, has been regularly published 6 issues per year (January-February, March-April, May-June, July-August, September-October and November-December). The aim is to provide medical knowledge, medical education, and other biomedical sciences information in various types of publications: original article, case report, and review article.

A Key focus of Vajira Med J is on basic and clinical science in urban medicine, including but not limited to epidemiology, etiology, pathogenesis, diagnosis and management for a better health of urban population.

Vajira Med J is a peer reviewed journal with an editorial policy of anonymous (when the reviewers' name are unrevealed) and blind review (when the authors' name are removed from the manuscript submitted for review). All submitted manuscripts are promptly assigned, by the Editor-in- Chief, to two or more members of the editorial board members who are expertise in the field to review the content in terms of ethics, methodology, accuracy, and clarity. In the event that the article is accepted, the corresponding author will receive 30 copies of the paper after it is published.

Submission of a manuscript implies that the article or any part of its essential substance, tables, or figures has not been previously published or not under consideration for publication elsewhere. This restriction does not apply to abstract or published proceedings to the scientific meetings, or an academic thesis. If accepted, it will not be published elsewhere in the same form, in Thai, English or in any other languages, without written consent from the Journal. The Editorial Board reserves the right to modify the final submission for editorial purposes. The intellectual content of the paper is the responsibility of the authors. The Editors and the Publisher accept no responsibility for opinions and statements of the authors.

Preparation of manuscripts

General requirements

All manuscripts can be submitted online (https://tci-thaijo.org/index.php/VMED and http://thailand.digitaljournals.org/index.php/VMJ/) or sent to email: sathit@nmu.ac.th 3 copies in print and on electronic data file via CD, diskette or email along with a cover letter and the checklist guideline. A cover letter must include name and title of the first or corresponding author, full address, telephone number, fax number, and e-mail address, title and category of the submitted manuscript: original article, case report, or review articles. The letter should contain the declared statements that the manuscript has been read and approved by all the authors in terms of the content and accuracy, and that the manuscript has not been previously published or is not under consideration for publication elsewhere. Previous publication in the form of abstract, published proceedings in the scientific meetings, or academic thesis is acceptable for a duplication or modification with an information (or declaration) to the editorial board. If applicable, a copy of ethics approval document should be sent along with the manuscript.

The article must be written in clear and concise Thai, or English. If the manuscript is written in Thai, English is allowed only when Thai word/phrase is unable to make the sentence clear. When English is used, lowercase letters are required. The numbers must be typed in Arabic. The text must be typed double-spaced, in single column, with 1 inch unjustified right margin on A4 paper. Cordial New in 16 pt. size is the preferred font style.

Checklist guideline for an author to submit a manuscript

To facilitate the manuscript preparation and submission, the authors must complete the checklist form and send it along with the manuscript. Any submitted manuscript without checklist form, incomplete data, or incorrect format will be returned to the corresponding author before proceeding. Checklist forms for various types of manuscript can be downloaded from Vajira Med J website (http://www.vajira.ac.th/vmj).

Manuscript Preparation

For researches which fit into any of the following study designs: randomized controlled, diagnostic test or observational studies should follow consort 2010 checklist, STARD checklist and STROBE checklist respectively. These checklists can be downloaded through our website.

The author should prepare the manuscript according to the Uniform Requirements for Manuscript Submitted to Biomedical Journals of the International Committee of Medical Journal Editors. (http://www.icmje.org/recommendations/). Briefly, the manuscripts should be structured in the following order: title and authors, abstract, main text, acknowledgments, and references.

1. **Title:** the title should be concise and suitable for indexing purposes. The first letter of each word should be in capital letter except for a preposition and an article.

2. **Authors:** all contributing author(s) with full name, graduate degree, and department and institutional affiliation of each author are required. E-mail address of the corresponding author should also be addressed.

3. **Abstract:** The abstract must be submitted in duplicate, both in Thai and English. Both Thai and English abstract should have similar or parallel contents. It should be concise and stand for the article. Tables, figures, or references are not included in

the abstract as well as the figures or results which do not appear in the article. A standard abstract in one paragraph without subheading is required for case report and review articles and should be limited to 300 words. Below the English abstract list 3-5 keywords for indexing purposes.

A structured abstract is required for original article. It must consist of 4 concise paragraphs under the headings: Objective(s), Methods, Results, and Conclusion(s). The **objective(s)** reflect(s) the purpose of the study, i.e. the hypothesis that is being tested. The **methods** should include the study design, setting of the study, the subjects (number and type), the treatment or intervention. The **results** include the salient outcome(s) of the study. The **conclusion**(s) state(s) the significant results of the study.

4. Main text: The text should be structured with the headings of **introduction, methods, results, and discussion** for original articles, and of **introduction, case report, discussion and conclusion** for case report. Review articles should have heading appropriate for the article.

The **introduction** should state clearly the objective(s) and rationale for the study and cite only the most pertinent references as background. The **methods** should include study design, subjects with inclusion and exclusion criteria, material, methods and procedures utilized with enough details for the study to be repeated, sample size calculation, and the statistical software and methods employed. The **results** should describe the study sample and data analyses to answer the objectives. There should be no more than 5-7 figures and tables (total) per manuscript. For the table, only horizontal lines above and below the heading and at the bottom of the table are made without any column line. The figures used should be original, any modification from other sources should be clearly indicated and state the site of the origin with written permission. If any photographs of the patients are used, they should not be identifiable or the photographs should be accompanied by written permission to use them. The **discussion** should briefly summarize or emphasize the main findings, interpret or explain their findings in comparison with other reports, state any limitation of the study, describe an impact on healthcare if any, and comment on the potential for future research.

5. Conflict of interest: the authors should declare the conflict of interest in the cover letter.

6. Acknowledgments: the authors should include only those who have made a valuable contribution to the work presented but who do not qualify as authors. This may include an involved patient population and any grant support.

7. References: state the references consecutively in the order in which they are first mentioned in the text. Use arabic numerals in superscription without parenthesis for reference in the text. Unpublished data and personal communications is not allowed. Published abstracts can be used as numbers references; however, reference to the complete published article is preferred. The references should be upto- date in that subject and be no more than 30 references for original articles. The 'Vancouver style' of references must be applied. List all authors when there are 6 or fewer, and list the first 6 and add 'et al' when there are 7 or more authors. Please refer to further detail of the reference format in the NEJM or official website of our journal.

Examples:

Journals

Tangjitgamol S, Hanprasertpong J, Manusirivithaya S, Wootipoom V, Thavaramara T, Buhachat R. Malignant ovarian germ cell tumors: clinico-pathological presentation and survival outcomes. Acta Obstet Gynecol Scand. 2010; 89: 182-9.

Books

Straus SE, Richardson WS, Glasziou P, Haynes RB. Evidence based medicine: how to practice and teach EBM. 3rd ed. Edinburgh: Churchill Livingstone; 2005. p.10-5.

Chapter in Books

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p.93-113.

Published proceedings paper

Berger H, Klemm M. Clinical signs of gastric ulcers and its relation to incidence [abstract]. In: Chuit P, Kuffer A, Montavon S, editors. 8th Congress on Equine Medicine and Surgery; 2003 Dec 16-18; Geneva, Switzerland. Ithaca (NY): International Veterinary Information Service (IVIS); 2003. p. 45.

Electronic journals/data

International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals [Internet]. 2014 [updated 2014 Dec 1; cited 2015 Jan 30] Available from: http://www.icmje.org/icmje-recommendations.pdf.

Thesis

Liu-Ambrose TY. Studies of fall risk and bone morphology in older women with low bone mass [dissertation]. [Vancouver (BC)]: University of British Columbia; 2004. 290 p.

Manuscript revision

All comments or queries returned to the authors for a revision or clarification should be thoroughly addressed or revised accordingly. The revised manuscript must be underlined or highlighted for the changes, and re-submitted, preferably, within four weeks to prevent a delay of a final decision. A maximum of 12 weeks is allowed for a revision or the editorial board will take the right to withdraw the manuscript from the submission system. The original manuscript must be returned along with the printed and electronic revised version. An accompanying summarized letter of revision point by point may expedite the re-review.

วชิรเวชสาร
และวารสารเวชศาสตร์เขตเมือง
Vajira Medical Journal:
Journal of Urban Medicine

ปีที่ 66 ฉบับที่ 6 พฤศจิกายน - ธันวาคม พ.ศ. 2565 Vol. 66 No. 6 November - December 2022

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นิพนธ์ต้นฉบับ (Original Articles)

วชิรเวชสาร
และวารสารเวชศาสตร์เขตเมือง
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Journal of Urban Medicine

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สารบัญ

หน้า

Age-Related Neck Circumference in Habitually Snoring Children: A Potential Screening Tool for Obstructive Sleep Apnea in Children

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Abstract

Objective: Neck circumference (NC) is becoming useful for various diseases in adults but not children. Due to a lack of normalized data. This study uses the normalized NC to compare with a patient's NC as a percentage (%NC) in habitually snoring children to distinguish obstructive sleep apnea (OSA) cases. The ratio of NC and adenoid thickness (NCAR) is hypothetically less in non-overweight OSA children. We proposed this ratio as a parameter to identify OSA in non-overweight children.

Methods: Habitually snoring children who underwent overnight pulse oximetry (overnight SpO_2)/ polysomnography (PSG) were eligible. Data gathering included an assessment of participants' body sizes and AT (from radiographs).

Results: Overall, there were 73 children (65% boys, median age 10.6 y (IQR 7.4-12.7), 52.1% of whom tested positive by either test. In addition, 58.9% of children underwent overnight SpO_2, and 20.9% tested positive. Among 30 children tested by PSG, confirmation of OSA diagnosis of varying severity was 96.7%. The positive and non-positive groups did not have statistically significant differences in %NC. In overweight children (n=40), there were no statistically significant differences of %NC between positive (n=27) and non-positive (n=13) results [94.9 (88.3-104.1) vs. 93.4 (89.3-104.4), p-value 0.669]. But the non-overweight group, positive children (n=19) had a statistically smaller median NCAR compared to non-positive children (n=11); 14.3 (12.7-14.9) vs. 16.2 (14.7-20.3), p-value=0.006. The proposed cut-off NCAR value in predicting non-positive tests in non-overweight children is more than 13.95, with a 47.4% sensitivity and 100% specificity. The positive predictive value is 100%, and the negative predictive value is 68.6%.

Conclusion: There was no statistically significant difference in %NC of the overall OSA vs. non-OSA children and the overweight OSA vs. non-OSA children. In the non-overweight group, NCAR was significantly smaller in positive children.

Keywords: neck circumference, habitual snoring, children, obstructive sleep apnea, screening

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เส้นรอบวงคอตามเกณฑ์อายุในเด็กที่นอนกรนประจำมีศักยภาพเป็นเครื่องมือคัดกรองภาวะหยุดหายใจขณะหลับจากการอุดกั้นในเด็กหรือไม่

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บทคัดย่อ

วัตถุประสงค์: เส้นรอบวงคอ (NC) มีประโยชน์สำหรับโรคต่าง ๆ ในผู้ใหญ่แต่ไม่ใช่ในเด็กเนื่องจากขาดข้อมูลที่เป็นค่ามาตรฐานตามเกณฑ์อายุ การศึกษานี้ใช้ค่า NC ตามเกณฑ์อายุของเด็กเพื่อเปรียบเทียบกับค่า NC ของผู้ป่วยเด็กนอนกรนประจำเป็นร้อยละ (%NC) เพื่อแยกภาวะหยุดหายใจขณะหลับจากการอุดกั้น (OSA) นอกจากนี้ในเด็ก OSA ที่ไม่มีโรคอ้วน อัตราส่วนของ NC กับความหนาของต่อมอะดีนอยด์ (NCAR) อาจใช้เป็นพารามิเตอร์ที่ช่วยแยกเด็ก OSA ได้ ผู้วิจัยจึงทำการศึกษาอัตราส่วนนี้ในเด็กกลุ่มนี้ด้วย

วิธีดำเนินการวิจัย: เด็กนอนกรนประจำอายุ 5-15 ปี ที่ได้รับการตรวจความอิ่มตัวก๊าซออกซิเจนในเลือดข้ามคืน (overnight SpO_2) หรือตรวจการนอนหลับ (polysomnography) จะถูกวัดขนาดร่างกาย ความยาวรอบคอ และความกว้างของต่อมอะดีนอยด์จากภาพรังสี

ผลการวิจัย: เด็กนอนกรนประจำทั้งหมด 73 คน (เพศชาย ร้อยละ 65 มัธยฐานอายุ 10.6 ปี (IQR 7.4-12.7) โดยร้อยละ 52.1 ของเด็กทั้งหมดให้ผลบวกต่อการตรวจวิธีใดวิธีหนึ่ง มีเด็ก ร้อยละ 58.9 ของทั้งหมดตรวจโดยวิธี overnight SpO_2 และให้ผลบวก ร้อยละ 20.9 ในจำนวนเด็ก 30 คนที่ทดสอบโดย PSG ยืนยันการวินิจฉัย OSA ร้อยละ 96.7 โดย ร้อยละ (%NC) ในเด็กทั้งหมด กลุ่มที่ผลการตรวจเป็นบวกและไม่เป็นบวกไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ เมื่อพิจารณาเฉพาะเด็กเริ่มอ้วน (overweight, n=40) ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติของร้อยละ (%NC) ระหว่างกลุ่มที่ผลเป็นบวก (n=27) กับไม่เป็นบวก (n=13) [94.9 (88.3-104.1) vs. 93.4 (89.3-104.4) ค่า p=0.669] แต่ในกลุ่มที่น้ำหนักตามเกณฑ์ เด็กที่ผลเป็นบวก (n=19) มีค่ามัธยฐาน NCAR น้อยกว่ากลุ่มที่ไม่เป็นบวก (n=11) อย่างมีนัยสำคัญทางสถิติ (n=11); 14.3 (12.7-14.9) vs. 16.2 (14.7-20.3), p-value=0.006 การทดสอบ ROC ของค่า NCAR พบว่า ค่า NCAR ที่มากกว่า 13.95 สามารถทำนายโอกาสที่ผลตรวจจะไม่เป็นบวกในเด็กที่น้ำหนักตามเกณฑ์ได้โดยมีความไวร้อยละ 47.4 และความจำเพาะร้อยละ 100 ค่าการทำนายเชิงบวกคือ ร้อยละ 100 และค่าการทำนายเชิงลบคือร้อยละ 68.6 ซึ่งเป็นกลุ่มที่น่าจะได้ประโยชน์จากการตรวจ PSG มากกว่า overnight SpO_2

สรุป: ไม่พบความแตกต่างที่มีนัยสำคัญทางสถิติของร้อยละ (%NC) ในเด็กระหว่างกลุ่มที่เป็น OSA และไม่เป็น OSA ทั้งในภาพรวมและเฉพาะในกลุ่มเด็กอ้วน แต่ในเด็กที่ไม่อ้วน เด็กที่ให้ผลการตรวจเป็นบวกจะมี NCAR เล็กกว่าอย่างมีนัยสำคัญทางสถิติ

คำสำคัญ: เส้นรอบวงคอ นอนกรน เด็ก ภาวะหยุดหายใจขณะหลับจากการอุดกั้น คัดกรอง

วันที่รับบทความ 7 พฤศจิกายน 2565 **วันแก้ไขบทความ** 30 พฤศจิกายน 2565 **วันตอบรับบทความ** 1 ธันวาคม 2565

Introduction

Sleep-related breathing disorders are clinically diverse disorders cover the spectrum from habitual snoring, upper airway resistance syndrome, obstructive hypoventilation, to obstructive sleep apnea (OSA). In Thailand, the prevalence of habitual snoring in children is 6.9-8.5% and OSA diagnosis is 0.7-1.3%[1-2]. However, a study of the OSA prevalence in children undergoing polysomnography (PSG) at a university hospital in Thailand was 92.7%[3]. The guidelines for diagnosis and treatment of snoring children who have enlarged tonsils and/or adenoids are available from the Thai Society of Pediatric Respiratory and Critical Care. According to the guidelines, the gold standard for OSA diagnosis is PSG, and the screening method is overnight pulse oximetry (overnight SpO_2)[4]. The guideline also recommended overnight SpO_2 as an alternative tool for OSA diagnosis because this test has a high positive predictive value. However, patients who test negative should further perform PSG because it has a high false negative rate of 47%[5].

Recently, more diseases are requiring the measurement of neck circumference (NC). In adults, increased NC is associated with OSA[6]. In women, and men who had NC greater than 16 and 17 inches, respectively, the risk of OSA increased[7]. A screening test called "STOP-BANG" in adult patients also used NC, body mass index (BMI), and symptoms[8]. In 2016, the NC was used in terms of the NC to height ratio (NHR) to assess OSA risk in pediatric and adult patients[9]. Results showed that children with an NHR > 0.25 (corrected for BMI z-score) had a 3.47-fold increased risk of OSA compared with an 18-fold increased risk of OSA in adults. Researchers speculated that this was due to the lack of age-related normalized NC in children. The problem with implementing the NC in children is that not only does the NC change with nutritional status, but also, the nature of growth of the NC in children makes implementation difficult.

In Thailand, normalized NC has already been made available for children of all ages and sexes[10]. If there is a difference between normalized NC of OSA and non-OSA children, this has potential as a screening tool for OSA. We hypothesized that overweight children with OSA tend to have greater NC than normal-weight children of the same age and are more likely than NC in overweight children without OSA. In contrast to non-overweight children whose NC should be average, the enlarged adenoids and tonsils are likely to cause OSA. When calculating the ratio between their average NC and their large adenoid thickness (AT) on radiographs, the values should be lower than in non-OSA children (who are supposed to have smaller adenoids). If the results are consistent with these assumptions; we could use the NC as an appropriate and cost-effective tool to select snoring children for PSG.

Methods

The primary objective of this cross-sectional study was to compare the mean age-related NC (%NC) of children with habitual snoring aged 5-15 years with and without OSA at Taksin Hospital, Bangkok, in 2018-2019. Secondary objectives were to compare the mean %NC in overweight children with and without OSA and compare the mean NC to the radiographic adenoid thickness (NCAR) ratio in non-overweight children with and without OSA. This research calculates the sample from the formula;

$$n \geq (1+r/r)(Z_{1-\alpha/2} + Z_{1-\beta})^2 / d^2 + Z^2_{1-\alpha/2}/2(1+r)$$

While n=sample size, r=sample size ratio assigned as 2, d=expected sample assigned as 0.8 (from the results of similar studies, $Z_{1-\alpha/2}$=two-sided Z value assigned as 1.96, $Z_{1-\beta}$=power assigned as 80%. Dependent variables are OSA occurrences either diagnosed by PSG or overnight SpO_2 monitoring[13]. Independent variables are age, sex, weight, height, socioeconomic status, household smoking, enlarged tonsils, chronic sinusitis, NC and thickness of adenoid glands from radiographs. The Bangkok Metropolitan Administration Human Research Ethics Committee approved the study protocol. Consent from parents or guardians was usually a prerequisite for participants. Adolescents received

the written assent forms. The patient's demographic data collection included age, sex, household smoking, physician's diagnosis of adenotonsillar hypertrophy, and physician's diagnosis of chronic sinusitis.

Inclusion criteria included children aged 5-15 years who had habitual snoring (history of snoring >3 nights/week) or breathing problems during sleep for whom a physician considered additional evaluation by performing either an overnight SpO_2 or PSG test. The choice of testing method for each participant is at the physician's discretion. This is greatly influenced by the patient's health insurance coverage.

Exclusion criteria: 1. suspected central apnea or central hypoventilation; 2. severe neuromuscular disorders (e.g., muscular dystrophy, cerebral palsy); 3. chronic pulmonary disease requiring home oxygen therapy; 4. facial proportions abnormalities such as Down syndrome; 5. inherited disorders of muscle tone such as Prader-Willi syndrome; and 6. CPAP titration patients with a tracheostomy tube or PSG after tracheostomy decannulation.

Measurements

On the overnight SpO_2 or PSG examination date, nurses who trained for the NC measurement measured the body sizes of participants, including weight (by Tanita® WB-100), height (by Seca® 216), and NC (by medical plastic measuring tape). A radiograph of the neck lateral soft tissue technique was obtained on the same date for measuring adenoid thickness (AT). Weight was measured with light clothing and without shoes. The comparison of patient weight and the weight according to the height standard for Thai children[11] is the %ideal weight [%ideal weight = patient weight x 100/ weight standard at P50]. The percentage of patient height compared with P50 of children of the same age is the %median H/A [%median H/A = patient height x 100/height standard at P50].

NC is the length around the base of the neck above the clavicle (according to the standard measurement of body proportions in Thai children)[10]. The age-related neck circumference (%NC) refers to the determined NC values calculated as a percentage compared with the NC of normal children of the same age and gender according to the formula [%NC = (measured NC x 100)/standard NC of children]. NCAR is the ratio between the measured NC and the thickness of the adenoids on radiographs. Adenoid thickness (AT) is the thickness of adenoids from the perpendicular to the most distant part (convex) of the gland to the line joining the upper end of the pterygomaxillary fossa and the tip of the anterior margin of the atlas bone[12]. The Digital Radiographic Viewer (PACS™) is used to measure AT using the measurement features provided in the software by the research project leader.

Obstructive sleep apnea (OSA) in children is a condition in which a child has complete obstruction of the upper airway during sleep so that air cannot enter through the nose or mouth. Respiratory flow measured by the thermistor has decreased by 90% or more in at least two respiratory cycles, accompanied by dyspnea and paradoxical movements of the chest and abdomen[13]. The PSG in this study, using Compumedic™Somte, consisted of standard full night PSG measurements in which trained sleep technicians monitored the patients' condition. The trained physicians evaluate polysomnograms regarding pediatric OSA diagnostic criteria[13]. Overnight SpO_2 is the oxygen saturation monitoring during sleep for at least 6 hours (using the Bitmos™ sat 805). The SpO_2 tracing was graphed using Satview™ software version 1.1.9 and interpreted using McGill oximetry scores[14]. The OSA diagnostic criteria used in this study were the apnea-hypopnea index (AHI) $\geq$ 1.5 events/hour (from PSG) or the oximetry score > 1 (from overnight SpO_2). The severities of OSA in children classified by AHI are AHI 1.5 to < 5 events/hour = mild OSA, AHI 5-10 events/hour = moderate OSA, and AHI > 10 events/hour = severe OSA[15]. If overnight SpO_2 results are negative or inconclusive and further PSG testing is required, this further testing involves another visit for analysis (using the same case number, the body sizes are

measured again and analyzed separately for each OSA test). Pediatric overweight diagnosis is made for a child with a percentage of %ideal weight ≥ 120%[16].

Statistical Analysis

All study participants with adequate sleep duration according to sleep monitoring standards were analyzed. However, this study did not find participants with insufficient sleep duration to be excluded. Most of the variables in this study followed a non-normal distribution by the Kolmogorov-Smirnov test, the reported results were given in term of the median (interquartile range (IQR): 25th to 75th percentile). Researchers used the Mann-Whitney U or Kruskal Wallis test for continuous variables comparison, and the test for categorical variables was the chi-square test. The analysis of correlation in this study was conducted via the Spearman test. The ROC analysis was for determining the optimal cutoff value from the potential variables. P values were two-sided and statistical significance was assumed at $p < 0.05$. The computer software for data analysis is SPSS for Windows version 16.0.

In data analysis, the researchers classify patients who perform overnight SpO_2 into groups of those who test positive and those who do not test positive (including inconclusive and negative patients). The rationale is that patients who do not give a positive result still need to be tested further with PSG because the overnight SpO_2 test has a high false negative value[5].

Results

A total of 73 Thai children with habitual snoring participated in the study; 65% were boys with a median age of 10.6 years. (IQR: 7.4-12.7) The total number of patients who tested positive for either PSG or overnight SpO_2 was 52.1%. There were 43 children (58.9%) who underwent overnight SpO_2. For children tested by overnight SpO_2 testing, 53.5% were negative, and 20.9% were positive. Among 30 children tested by PSG, confirmation of OSA diagnosis of varying severity was 96.7%. In the PSG group, only one patient had negative results (3.3%). The demographic and clinical characteristics of the patients tested with overnight SpO_2 and PSG are shown in Table 1. The overnight SpO_2 patients had a higher percentage of family history of household smoking than the PSG group. There is no statistically significant difference in demographic data between overweight children with and without OSA. In non-overweight participants, positive test group (n=22) significantly has more proportion of negative household smoking (90.9%) than non-positive patients (54.5), p-value 0.027.

Overall, the non-positive patients (n=35) comprised the negative PSG patients (n=1), negative overnight SpO_2 patients (n=23), and inconclusive overnight SpO_2 patients (n=11). Both groups showed no statistically significant difference in terms of AT, %ideal weight, %median H/A, BMI, %NC, and NCAR, as shown in Table 2. None of the non-positive overnight SpO_2 subjects proceed to perform PSG testing during the study period.

There were no statistically significant differences in the overnight SpO_2 group between various oximetry scores and the body size variables. Similarly, there were no statistically significant differences in the PSG group between the OSA severity by PSG and the body size variables. (table 3). However, there was a correlation between some anthropometric data and nadir SpO_2 or PSG indices. Nadir SpO_2 of all patients from both tests (PSG and overnight SpO_2) was statistically inversely related to AT. Meanwhile, AHI and RDI had a linear correlation with %median H/A and %NC, and CAI had a linearly inverse correlation with %ideal weight andBMI (table 4).

In the correlated variables plotted in the scatterplots, the variables with the highest r-squared (r^2) values were AHI vs. %NC ($r^2 = 0.226$) and RDI vs. %NC ($r^2 = 0.228$). (figure 1) The scatterplots between %median H/A vs. AHI and RDI had r^2 values of 0.106 and 0.107, respectively. The CAI was inversely related to the %ideal weight and BMI, with the r^2 values from the scatterplot being 0.018 and 0.037, respectively. The AT vs. nadir SpO_2 had r^2 values of 0.109.

Table 1 Demographic and clinical characteristics of patients who underwent overnight SpO_2 and PSG testing

Variables[a]	Overnight SpO_2 (n=43)		PSG (n=30)		p-value
Male (%)	67.4%		63.3%		0.804
Household smoker (%)	39.5%		16.7%		0.042
ATH diagnosis (%)	76.7%		73.3%		0.787
Chronic sinusitis diagnosis (%)	2.3%		3.3%		1.000
Age (year)	9.9 (8.1-11.3)		11 (6.7-13.3)		0.641
%ideal weight	128 (106-159)		131.5 (102.5-167.8)		0.340
%median H/A	102 (97-105)		101 (95.8-104)		0.777
BMI	20.6 (17.3-28.4)		23.4 (16.22-29.7)		0.713
AT	1.8 (1.6-2.1)		1.7 (1.3-2.3)		0.224
%NC	89.5 (84.1-96.4)		92.5 (81-99.3)		0.936
NCAR	16.2 (14.4-19.2)		16.7 (14.3-20.4)[b]		0.964
Sleep architecture • TST (min) • Latency (min) • N1 (% of TST) • N2 (% of TST) • N3 (% of TST) • REM (% of TST) • Efficiency (%)			469.5 (422-491.8) 11.5 (4.8-19.3) 4.5 (3-8.75) 46.5 (42.8-54.3) 26 (17.8-33) 18 (16.8-21) 92.7 (90.3-95.6)		
Events	Oximetry Score 1 Oximetry Score 2 Oximetry Score 3 Oximetry Score 4	79.1% 11.6% 4.7% 4.7%	Arousal index RDI CAI AHI	37.2 (24.5-49.7) 8.9 (4.4-16.1) 0.4 (0-1.25) 8.3 (3.8-16)	
Nadir SpO_2 (%)	91 (86.8-93)		89 (85.8-92)		0.111
ETCO2 > 45 mmHg (% of TST)			0.14±0.6[c]		
Diagnosis	Negative Inconclusive Positive	53.5% 25.6% 20.9%	1^0 snoring Mild OSA Moderate OSA Severe OSA	3.3% 30% 30% 36.7%	

[a]Numbers are in median (IQR: 25-75th percentile), [b]n=25 (Five patients had a history of adenotonsillectomy, and adenoid thickness is 0 mm).
[c]2 patients had ETCO2 > 45 of 1 and 2.6% of TST, Numbers are in mean+S.D. (ATH = adenotonsillar hypertrophy, TST = total sleep time, RDI = respiratory disturbance index, CAI = central apnea index, AHI = apnea-hypopnea index; all indices are in events/h)

Table 2 Comparisons of body sizes in participants according to test results in each method

Variables[a]	Positive			Non-positive			p-value		
	Overall (n=38)	Overnight SpO_2 (n=9)	PSG (n=29)	Overall (n=35)	Overnight SpO_2 (n=34)	PSG (n=1)	Overall (n=73)	Overnight SpO_2 (n=43)	PSG (n=30)
AT (cm)	1.76 (1.6-2.32)	2.1 (1.7-2.5)	1.64 (1.4-2.1)	1.79 (1.62-2.08)	1.78 (1.6-2)	2.3	0.685	0.161	0.533
%IBW	138 (102-172)	146 (108-184.5)	130 (102-165)	128 (106-158)	124 (105.7-151.3)	177	0.623	0.298	0.333
%H/A	101 (96-104)	100 (96-105.5)	101 (95.5-104)	102 (100-105)	102 (99.5-105)	102	0.205	0.502	0.867
BMI	24.6 (16.3-31.4)	27.85 (17.2-33.7)	23.2 (16.2-29.2)	20.6 (17.3-27.9)	20.6 (17.2-27.8)	34.6	0.600	0.418	0.267
%NC	93.5 (81.7-100.1)	93.5 (79.8-103.4)	90.7 (80.8-100.1)	89.5 (84.4-96.4)	89.3 (84.3-96.4)	94.6	0.727	0.714	0.733
NCAR (n=68)[b]	16.6 (14.3-19.5)	16.1 (13.8-17)	16.9 (14.3-20.5)	16.2 (14.7-19.6)	16.5 (14.6-19.8)	15.8	0.581	0.309	0.88

[a]Numbers are in median (IQR: 25th-75th percentile) [b]5 positive participants had an adenoid thickness of 0 mm. due to post-adenotonsillectomy (All were in the PSG group). (%IBW is %ideal weight, %H/A is % median H/A)

Table 3 Anthropometric variables between various overnight SpO_2 and PSG outcomes

Variables[a]	Overnight SpO_2					PSG				
	Ox. Score 1 (n=34)	Ox. Score 2 (n=5)	Ox. Score 3 (n=2)[b]	Ox. Score 4 (n=2)[b]	p-value	1^{o} snoring (n=1)	Mild OSA (n=9)	Moderate OSA (n=9)	Severe OSA (n=11)	p-value
AT (cm)	1.78 (1.61-2.04)	1.68 (1.47-2.2)	2.37±0.33	2.35±0.48	0.115	2.3	1.58 (0-2)	1.51 (0.7-1.8)	1.81 (1.6-2.4)	0.158
%IBW	124 (105.8-151.3)	173 (108-193)	122.5±3.3	149±4.7	0.539	177	115 (92.5-142.5)	133 (107.5-170.5)	144 (103-178)	0.185
%H/A	102 (99.5-105)	96 (96-105)	97.5±3.5	108.5±4.9	0.107	102	98 (93.5-101.5)	101 (95-107)	103 (100-104)	0.506
BMI	20.6 (17.2-27.8)	27.9 (16.9-43.9)	22.7±8.3	25±9.7	0.817	34.6	19 (14.2-25.3)	23.6 (17.6-30.5)	25.3 (16.2-30.9)	0.149
%NC	89.3 (84.3-96.8)	87.1 (78.9-103.4)	86.1±1.2	103.3±1.4	0.498	94.6	77.9 (76.5-96)	90.7 (87.9-99.7)	94.6 (89.8-101.7)	0.109
NCAR[c]	16.5 (14.6-19.8)	16.6 (14.7-22.2)	13.9±4.7	14.4±0.1	0.440	15.8	14.5 (12.4-16.8)	18.9 (17.2-21.6)	16.25 (14.3-20.6)	0.156

[a]Numbers are in median (25th-75th percentile) [b]Numbers are in mean±S.D. [c]5 patients in this group had a history of adenotonsillectomy, and adenoid thickness is 0 mm. (Ox. Score = oximetry score, RDI = respiratory disturbance index, CAI = central apnea index, AHI = Apnea-hypopnea index; all indices are in events/h)

Table 4 Correlation coefficients (p-value) between nadir SpO_2 or PSG indices and body sizes

	Nadir SpO_2 (N=73)	AHI (n=30)	RDI (n=30)	CAI (n=30)	Arousal index (n=30)
Adenoid thickness	-0.259 (0.027)	0.298 (0.109)	0.323 (0.082)	-0.059 (0.757)	0.338 (0.068)
%ideal weight	-0.198 (0.092)	0.346 (0.061)	0.347 (0.061)	-0.401 (0.028)	0.141 (0.458)
%median H/A	-0.031 (0.792)	0.374 (0.042)	0.371 (0.044)	-0.199 (0.293)	0.142 (0.454)
BMI	-0.185 (0.118)	0.345 (0.062)	0.346 (0.061)	-0.470 (0.009)	0.141 (0.458)
%NC	-0.075 (0.528)	0.465 (0.01)	0.467 (0.009)	-0.279 (0.135)	0.201 (0.287)
NCAR	0.186 (0.129)	0.053 (0.801)	0.054 (0.796)	-0.098 (0.641)	0.057 (0.786)

(AHI=Apnea-hypopnea index, RDI=respiratory disturbance index, CAI = central apnea index)

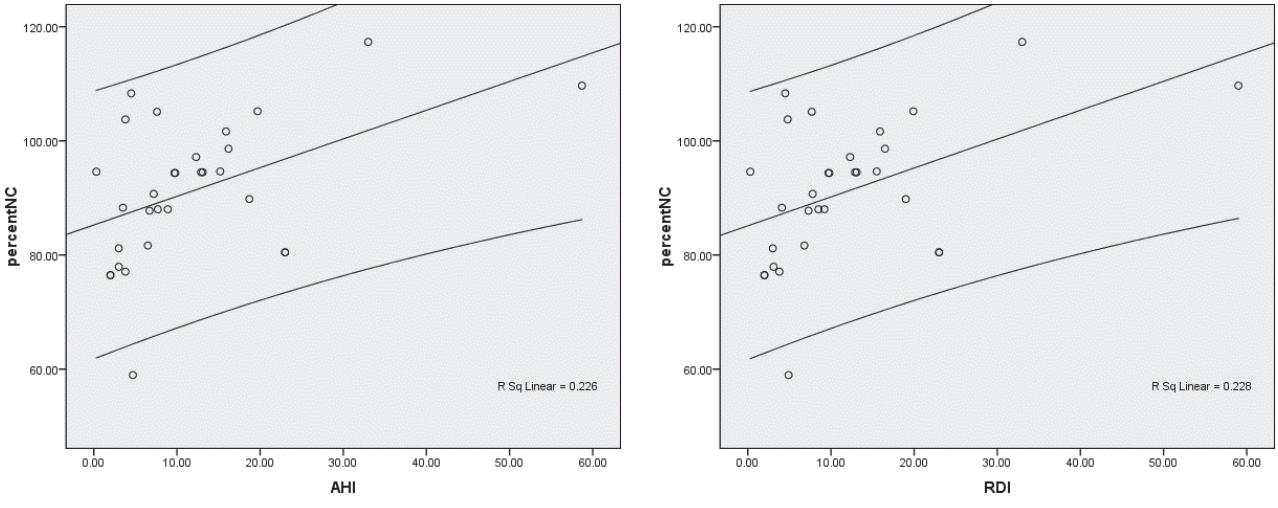

Figure 1 Correlation between %NC vs. AHI (left) and RDI (right)

The comparison of %NC in the overweight group (n=40), there were no statistically significant differences between positive (n=27) vs. non-positive (n=13) results [94.9 (88.3-104.1) vs. 93.4 (89.3-104.4), p-value 0.669]. But in the non-overweight group, positive children (n=19) had a statistically smaller median NCAR compared to non-positive children (n=11); 14.3 (12.7-14.9) vs. 16.2 (14.7-20.3), p-value 0.006. (3 non-overweight children were excluded from this analysis because they underwent adenotonsillectomy before this follow-up PSG. They had no residual radiographic adenoid hypertrophy).

ROC analysis of NCAR for predicting non-positive tests in the non-overweight children had the area under the curve of 0.799, p-value 0.007 (95%CI 0.64-0.958). The proposed cut-off NCAR value in predicting non-positive tests in non-overweight children is more than 13.95, with 100% specificity and 47.4% sensitivity. The positive and negative predictive values are 100% and 68.6%, respectively.

Discussion

This study found no statistically significant differences in body size between positive and non-positive patients (either PSG test or overnight SpO_2 test). However, there were correlations

between some anthropometric parameters and OSA indices or nadir SpO_2. For %NC in overweight children, we found no statistically significant differences between positive and non-positive patients. For NCAR in non-overweight children, we found that positive children statistically had a smaller median NCAR than non-positive children. According to this study, NCAR > 13.95 predicted non-positive tests in non-overweight children with high specificity and moderate sensitivity. When considering patients in the overnight SpO_2 group, there are no statistically significant differences between oximetry scores and body sizes. However, we found a correlation between AT and nadir SpO_2 in this group with a coefficient of -0.525 (p-value 0.0003). The reason for the non-significance between oximetry scores and AT is possibly due to the components of these scores. The oximetry scores comprise the nadir SpO_2 and the frequency of the SpO_2 drop. AT itself may not correlate with the latter factor. As with the PSG cohort, we did not find a statistically significant difference between OSA patients of varying severity and patients with primary snoring. However, there was only one in the primary snoring group in this study. When we excluded the primary snoring case, the body sizes (BMI, %ideal weight, and %NC) tended to increase as the severity increased. In particular, the %NC had the smallest p-value of 0.109, and %NC was statistically correlated to AHI and RDI.

Two previous studies had the same results as this study[17-18]. Both studies found no statistically significant difference in NC between OSA and non-OSA groups. However, the average age of patients from these two studies were different; one studied early school-age children[18], and the other studied adolescents[17]. Instead, they found that some ratios were significantly different between the OSA and non-OSA groups; one was the neck-to-height ratio[18], and the other was the waist-to-height ratio[17]. We hypothesize that a single parameter such as length, height, or circumference is not sufficiently sensitive to differentiate OSA children from non-OSA. In 2016, the use of NHR to assess OSA risk in pediatric and adult patients[9] found that children with an NHR > 0.25 (corrected for BMI z-score) had an increased risk of OSA but less than in adults (3.47- vs. 18-fold). Researchers speculated that this was due to the lack of age-related normalized NC in children. This study used age-related normalized NC to compare but failed to achieve the same result. The reason is probably that age-related normalized NC in this study is not a BMI z-score-corrected value.

In overweight children, %NC was not statistically significantly different between the OSA and non-OSA groups. Most of the past studies used raw NC values to determine the risk of OSA. One study found that children with NC > 95th percentile increased their risk of OSA statistically by 1.7 times, but the effect was insignificant for those under 12 years old[19]. In this study, we did not find the same result because when using the NC cut-off at the 95th percentile, this study found a relative risk of 1.09 (p-value 0.605, 95%C.I. 0.78-1.52). The reason is that children in this study were of a lower mean age than the mentioned study. The effect of NC in younger children might not be as pronounced as in the older group. In pre-teens with OSA, enlarged adenoids may play a greater role than overweight. In the non-overweight group, the children who tested positive had a statistically smaller median NCAR compared to the non-positive group. This study is the first to use NCAR to study its relationship with OSA. The ratios used in the previous studies were neck-to-waist (NWR)[17, 20] and neck-to-height (NHR) ratios[9]. Both ratios (NWR and NHR) work better in adolescents than in younger children, and in overweight children than non-overweight ones. Therefore, we were interested in variables among non-overweight children, so we proposed NCAR. However, we also analyzed NHR and NWR in this population and found no statistically significant differences between positive and non-positive patients. The reason might be that children in this study were predominantly early adolescents whose morphological changes were not similar to those in older adolescents who have had growth spurts

already. There was a statistically significant inverse relationship between CAI vs. %ideal weight and BMI. As in the previous study[21], central sleep apnea (CSA) incidence is higher than in adults, and overweight children had a lower incidence of CSA than non-overweight children. The same was true for this study.

This study is a pioneer study using NCAR in non-overweight children. OSA in children has a complex pathogenesis, especially in the overweight group. The previously mentioned studies have unsuccessfully found a single anthropometric parameter in identifying the OSA cases in children. In contrast to using ratios, the results are more promising. The rationale for using NCAR in the non-overweight group is also reasonable (the small neck circumference of the non-overweight divided by the thicker adenoids of suspected OSA cases, the result should be smaller than the non-OSA). We therefore strengthen the argument that NCAR has potential for screening OSA.

The possible cause of the failure to demonstrate statistically significant differences between positive and non-positive groups is that we have limited number of sample size and we found only one negative PSG subject to compare between groups. In Thailand, PSG is a test mostly performed in patients in which there is a high suspicion of OSA. Therefore, this selection bias give higher chances of a positive result than in the general population. And because overnight SpO_2 testing is more convenient than PSG testing and tends to be used more, especially in resource-constrained countries, then the researchers included diagnostic criteria of OSA from either overnight SpO_2 or PSG. As a result, the results of this study may not be directly compared with other studies in terms of OSA incidence. Even though overnight SpO_2 is often the preferred method for OSA screening in this institution due to its feasibility and cost-effectiveness, there will be a group of patients who have inconclusive results and need additional PSG testing. It would be great to have a variable(s) that can predict the probability of OSA in this group of patients and allow us to choose PSG instead of overnight SpO_2 testing. Unfortunately, this study showed no helpful parameter related to body size except the NCAR for non-overweight snoring children. The hypothesis of NCAR is reasonable for non-overweight children, but these populations were both overweight and non-overweight mixed in equal proportions, so the discriminant power of this value was not good in this case. The limitation of NCAR is in a patient who underwent adenoidectomy because it uses the thickness of the adenoid gland as the denominator, which is equal to zero, making it impossible to use in this group of patients who, on the basis of common sense, are unlikely to develop OSA due to this cause. Only nine children (12.3%) in this study were under six years of age, which is the age at which adenotonsillar hypertrophy is prominent and results in OSA[22]. We selected these children for analysis and found no statistically significant differences between all anthropometric variables and OSA test results. The explanation may be that the small number of cases in this age group may not be able to demonstrate the importance of AT in this study. Further studies in the 3–6-year age group should yield more reliable results. In this study, the location of the NC measurement was at the base of the neck. This location is the reference from the standard NC measurement[10]. Comparing the results of this study with others may need to consider this as a limitation.

In summary, anthropometric measurement as isolated value in “habitually snoring children” seems invaluable for the screening OSA. The utility of such parameters in ratios (such as NCAR, NWR, NHR) has greater potential as a screening tool. A well-designed study to validate NCAR utilization is necessary before generalizability in habitually snoring children. Greater sample sizes, especially in the PSG test group, are necessary to increase the number of negative cases for comparison. Alternatively, the randomization between PSG and overnight SpO_2 to evenly distribute the negative subjects in both groups might provide more reliable conclusions. Finally, future research should consider the relevance of puberty as a factor.

Conclusion

There was no statistically significant difference in %NC of the OSA and non-OSA children. In overweight children, there was also no statistically significant difference in %NC between positive and non-positive groups. In the non-overweight group, NCAR was significantly smaller in positive children than in non-positive children.

Conflict of interest

The authors declare that they have no conflict of interest.

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Prevalence and Risk Factors of Positional Obstructive Sleep Apnea (POSA) among Children with Obstructive Sleep Apnea

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Abstract

Objective: This study aimed to assess the prevalence and risk factors of positional obstructive sleep apnea (POSA) among children with OSA.

Methods: A retrospective study was conducted. One hundred and three children with OSA who were aged 3 to 18 years between April 2013 and July 2021 were included in this study. Demographic and polysomnographic data were gathered.

Results: The prevalence of POSA was 42.7%. No significant differences were observed in age, gender, tonsil score, weight status and medical comorbidities. Children with POSA had a significantly higher supine AHI than non-POSA (9.6 [0.0-98.7] versus 4.7 [0.0-55.4], $p = 0.012$). The median non-supine AHI of POSA was significantly lower than non-POSA (0.0 [0.0-18.6] versus 5.3 [0.0-78.9], respectively $p < 0.001$).

Conclusion: POSA among children with OSA occurs frequently, similar to adults with POSA. POSA is associated with higher supine AHI and lower non-supine AHI. Positional therapy might be beneficial in children with POSA.

Keywords: positional obstructive sleep apnea, obstructive sleep apnea, children

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ความชุกและปัจจัยเสี่ยงของเด็กที่มีภาวะหยุดหายใจขณะหลับจากการอุดกั้นที่ขึ้นกับท่านอน

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาความชุกและปัจจัยที่เกี่ยวข้องกับภาวะหยุดหายใจขณะหลับจากการอุดกั้นที่ขึ้นกับท่านอนในผู้ป่วยเด็กที่มีภาวะหยุดหายใจขณะหลับจากการอุดกั้น

วิธีดำเนินการวิจัย: งานวิจัยนี้เป็นการศึกษาแบบย้อนหลังโดยศึกษาในผู้ป่วยเด็กภาวะหยุดหายใจขณะหลับจากการอุดกั้น 103 คน อายุ 3 ปี ถึง 18 ปี ที่คณะแพทยศาสตร์วชิรพยาบาลระหว่างเดือนเมษายน พ.ศ. 2556 ถึงเดือนกรกฎาคม พ.ศ. 2564 โดยเก็บข้อมูลจากเวชระเบียนและผลการตรวจติดตามการนอนหลับ

ผลการวิจัย: ภาวะหยุดหายใจขณะหลับจากการอุดกั้นที่ขึ้นกับท่านอนคิดเป็นร้อยละ 42.7 ไม่พบความสัมพันธ์ของอายุ เพศ ขนาดต่อมทอนซิล น้ำหนักตัว โรคประจำตัวกับภาวะหยุดหายใจขณะหลับจากการอุดกั้นที่ขึ้นกับท่านอน โดยพบค่าเฉลี่ยของจำนวนที่หยุดหายใจและหายใจแผ่วแสดงในท่านอนหงาย (supine AHI) สูงในผู้ป่วยเด็กภาวะหยุดหายใจขณะหลับจากการอุดกั้นที่ขึ้นกับท่านอน (POSA) เมื่อเปรียบเทียบกับเด็กที่ไม่มีภาวะหยุดหายใจขณะหลับจากการอุดกั้นที่ขึ้นกับท่านอน (non-POSA) (9.6 [0.0-98.7] และ 4.7 [0.0-55.4], p = 0.012) และค่าเฉลี่ยของจำนวนที่หยุดหายใจและหายใจแผ่วแสดงในท่านอนอื่น ๆ (non-supine AHI) ในผู้ป่วยเด็กภาวะหยุดหายใจขณะหลับจากการอุดกั้นที่ขึ้นกับท่านอน มีค่าต่ำกว่าเมื่อเปรียบเทียบกับเด็กที่ไม่มีภาวะหยุดหายใจขณะหลับจากการอุดกั้นที่ขึ้นกับท่านอน (0.0 [0.0-18.6] และ 5.3 [0.0-78.9], p < 0.001)

สรุป: ภาวะหยุดหายใจขณะหลับจากการอุดกั้นที่ขึ้นกับท่านอนในเด็กพบได้บ่อย ซึ่งอุบัติการณ์ใกล้เคียงกับภาวะหยุดหายใจขณะหลับจากการอุดกั้นที่ขึ้นกับท่านอนในผู้ใหญ่ ซึ่งสัมพันธ์กับค่าเฉลี่ยของจำนวนที่หยุดหายใจและหายใจแผ่วแสดงในท่านอนหงายที่มีระดับสูง และค่าเฉลี่ยของจำนวนที่หยุดหายใจและหายใจแผ่วแสดงในท่านอนอื่น ๆ ในระดับต่ำ การรักษาโดยปรับท่านอนน่าจะเป็นประโยชน์ในภาวะหยุดหายใจขณะหลับจากการอุดกั้นที่ขึ้นกับท่านอนในเด็ก

คำสำคัญ: ภาวะหยุดหายใจขณะหลับจากการอุดกั้นที่ขึ้นกับท่านอน ภาวะหยุดหายใจขณะหลับจากการอุดกั้นในเด็ก

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Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent upper airway obstruction associated with intermittent nocturnal hypoxia and sleep disruption. OSA occurs in 1- 4% of healthy children, while the prevalence of OSA among children with comorbidities such as obesity, craniofacial malformation, and Down syndrome is 60-80%[1-3]. There is evidence that body position during sleep can affect the severity of OSA. This is known as positional obstructive sleep apnea (POSA), present predominantly in the supine sleeping position[4]. POSA is defined by a supine apnea-hypopnea index (AHI) at least twice in a non-supine position[5]. Studies for POSA in children are limited. It has been established that 19% of children with OSA and 58% of obese children with OSA have POSA, while 55% of adults with OSA have POSA[6-8]. Several factors may affect the sleep position on OSA severity, including age, obesity, and history of adenotonsillectomy (A&T)[9-10]. A&T is the first line of management for children with OSA, but the success rate is only 51% for both obese and non-obese children[11]. Continuous positive pressure therapy (CPAP) is the main therapy for persistent OSA in children following A&T. However, adherence rates to CPAP are low[12]. There are alternative treatments for POSA in children, such as positional therapy[13]. This study aimed to evaluate the prevalence of POSA and identify the factors associated with POSA in children.

Methods

Study design and participants

This was a retrospective study performed with 151 children at the Vajira Sleep Center, Navamindradhiraj University from April 01, 2013 to July 31, 2021. One hundred and three patients aged between 3-18 years undergoing a baseline diagnostic polysomnogram (PSG) with a diagnosis of OSA were included in the study. The criteria used for diagnosis of OSA is the obstructive apnea-hypopnea index (AHI) > 1/h; further delineating the severity as mild OSA (AHI > 1-5/h), moderate OSA (AHI > 5-10/h), and severe OSA (AHI > 10/h). The exclusion criteria included patients with only a supine position, a PSG-measured total sleep time (TST) of less than 6 hours, and subjects with bradycardia or tachycardia.

Data acquisition

Data collection from the medical records and PSG results included age, gender, weight, height, tonsil size, underlying disease, total sleep time (TST), total AHI, supine AHI, non-supine AHI, mean oxyhemoglobin saturation (SpO_2), and minimal SpO_2.

Weight status determinations (normal weight, overweight, and obesity) were made using the median weight-for-height on growth charts from the Department of Health, Ministry of Public Health, Thailand[14]. According to definitions from the Ministry of Public Health, obesity is defined as a median of weight-for-height > median +3 SD, overweight as a median of weight-for-height ≤ median +3 SD and > median +2 SD, and normal weight as a median of weight-for-height ≤ +2 SD and ≥ -2 SD. Tonsils were graded from 0-4 by Brodsky[15]. Subjects were divided into three age groups: < 6 years, 6-12 years, and > 12 years. Medical comorbidities were categorized as respiratory diseases including allergic rhinitis and asthma, cardiovascular diseases including hypertension and valvular heart disease, and neurological disorders including epilepsy, Down syndrome and attention deficit hyperactivity disorder.

POSA is defined by a supine AHI at least twice that in a non-supine position. PSG includes electroencephalography (EEG), electro-oculography, submental and anterior tibialis electromyography, electrocardiography, oronasal airflow, thoracoabdominal movement, positions, snoring, and oxygen saturation. PSG was attended by a trained sleep technician. Sleep staging and respiratory scoring were interpreted by sleep physicians using the criteria defined by the American Academy of Sleep Medicine[16]. The AHI was defined as the combined number of apneas and hypopneas recorded per hour of sleep. Apnea was defined as when the peak

signal excursions decreased by more than 90% of the pre-event baseline for at least two breaths. Hypopneas were defined as the peak signal excursions being decreased by more than 30% of the pre-event baseline for at least two breaths and were associated with more than 3% oxygen desaturation or EEG arousal[16].

Statistical analysis

Descriptive statistics were described as frequencies and percentages for categorical variables. Continuous variables were presented as means ± standard deviation or median (range) when the variables were not distributed normally. A Chi-square test was performed for analyzing the categorical variables. The differences in continuous variables between POSA and non-POSA were compared using the independent sample t-test and Mann-Whitney test with a significance level set at $p < 0.05$. All statistical analyses were performed using SPSS version 28.0 (IBM Corporation, Armonk, NY).

Results

One hundred and three children were enrolled in this study, including 78 males (75.7%), and the mean age was 8.45 ± 3.93 years old. Most of the children were from 6 to 12 years old (55.3%). In these children, tonsil grade 3 was 42.7% (49) and grade 4 28.2% (29). Children who were obese and overweight accounted for 43.7% (n=45) and 9.7% (n=10), respectively. Among these, 44 (42.7%) fulfilled the criteria for POSA, and 59 (57.3%) were non-POSA. Demographic data are given in Table 1.

We classified 103 children based on OSA severity; 38 (36.9%) were categorized as mild OSA, 29 (28.2%) were moderate OSA, and 36 (35%) were severe OSA. Overall, the median total AHI was 6.6 (1.3-98.7) events/hr. PSG data are summarized in Table 2.

Table 1 Demographic data (n=103)

Characteristics	Mean ± SD
Age in years	8.45 ± 3.93
Weight in kg	46.52 ± 30.09
Height in cm	133.47 ± 23.24
Tonsil score size, n (%)	
0	2 (1.9)
1	10 (9.7)
2	18 (17.5)
3	44 (42.7)
4	29 (28.2)
Gender, n (%)	
Male	78 (75.7)
Female	25 (24.3)
Medical comorbidities, n (%)	
Respiratory disease	12 (11.7)
Cardiovascular disease	12 (11.7)
Neuro-psychiatric disease	6 (5.8)

Table 2 Polysomnographic data (n=103)

Sleep study parameters	Mean ± SD
TST (min)	443.88 ± 72.66
Total AHI (events/hr.), median (range)	6.6 (1.3-98.7)
Supine AHI (events/hr.), median (range)	7.0 (0.0-98.7)
Non-supine AHI (events/hr.), median (range)	3.9 (0.0-78.9)
Mean SpO_2 (%)	95.36 ± 8.92
Minimal SpO_2 (%)	83.20 ± 9.23

The mean age of POSA and non-POSA was 8.52 ± 0.62 and 8.38 ± 0.49 years, respectively. Thirty-five males and nine females were POSA. The median total AHI for POSA and non-POSA were 8.7 (2.0-98.7) and 5.3 (1.3-54.9) events/hr., respectively. There were no significant differences between the POSA group and the non-POSA group in terms of age, weight, height, tonsil score, gender, medical comorbidities, TST, total AHI, mean SpO_2, and minimal SpO_2. The non-supine AHI was significantly lower in children with POSA (0.0 [0.0-18.6] versus 5.3 [0.0-78.9], $p < 0.001$). There was a trend for the POSA group to have a higher supine AHI compared with the non-POSA group (9.6 [0.0-98.7] versus 4.7 [0.0-55.4], $p = 0.012$). Comparison characteristics and PSG data between POSA and non-POSA are shown in Table 3.

There was found to be an increase in POSA with older age (52.94%), being overweight or obese (44.82%), and moderate to severe OSA (47.69%). No significant difference was found for the age group, weight status and OSA severity between children with POSA and without POSA. Data for age group, weight status, and OSA severity are shown in Table 4.

Table 3 Baseline characteristics and polysomnographic comparison between POSA and non-POSA

	POSA (n=44)	Non-POSA (n=59)	*p* value
Age (year)	8.52 ± 0.62	8.38 ± 0.49	0.866
Weight (kg)	47.67 ± 32.42	45.66 ± 28.47	0.739
Height (cm)	135.31 ± 23.42	132.10 ± 23.20	0.490
Tonsil score, n (%)			0.452
0	1 (2.3)	1 (1.7)	
1	6 (13.6)	4 (6.8)	
2	7 (15.9)	11 (18.6)	
3	15 (34.1)	29 (49.2)	
4	15 (34.1)	14 (23.7)	
Gender, n (%)			0.435
Male	35 (79.5)	43 (72.9)	
Female	9 (20.5)	16 (27.1)	
Underlying disease, n (%)			0.923
Respiratory disease	5 (38.4)	7 (41.2)	
Cardiovascular disease	6 (46.2)	6 (35.3)	
Neuro-psychiatric disease	2 (15.4)	4 (23.5)	
TST (min)	429.15 ± 91.83	452.88 ± 57.06	0.140
Total AHI (events/hr.), median (range)	8.7 (2.0-98.7)	5.3 (1.3-54.9)	0.191
Supine AHI (events/hr.), median (range)	9.6 (0.0-98.7)	4.7 (0.0-55.4)	0.012
Non-supine AHI (events/hr.), median (range)	0.0 (0.0-18.6)	5.3 (0.0-78.9)	<0.001
Mean SpO_2 (%)	94.50 ± 13.50	96.01 ± 1.93	0.396
Minimal SpO_2 (%)	83.18 ± 7. 88	83.21 ± 10.19	0.986

Table 4 Comparison of POSA and Non-POSA in different age group, weight status and OSA severity

Data	POSA (n=44)	Non-POSA (n=59)	*p* value
Age, n (%)			0.645
< 6 years	12 (27.3)	17 (28.8)	
> 6-12 years	23 (52.3)	34 (57.6)	
> 12 years	9 (20.4)	8 (13.6)	
Weight status defined by weight-for-height, n (%)			0.830
Obesity	21 (47.7)	27 (45.8)	
Overweight	5 (11.4)	5 (8.4)	
Normal weight	18 (40.9)	27 (45.8)	
OSA severity, n (%)			0.409
Mild	13 (29.6)	25 (42.4)	
Moderate	14 (31.8)	15 (25.4)	
Severe	17 (38.6)	19 (32.2)	

Discussion

In our study, the prevalence of POSA was 42% among children with OSA (when defined as obstructive events occurring twice as often in the supine than non-supine sleep position). Nisbet et al. also showed that children aged 0-18 years who were positional patients when using at least twice the AHI in one sleep position than other position and high supine AHI were 31% and 54%, respectively[17]. The prevalence of POSA was estimated at approximately 55% among adults with OSA[8,18].

The definition of POSA establishes various criteria. Cartwright et al. described that POSA is defined as a difference of ≥ 50% in obstructive AHI between supine and non-supine positions[5]. Marklund et al. defined supine-dependent sleep apnea as a supine AHI more than 10 with lateral AHI less than 10[19]. Mador et al. suggested that POSA is defined as AHI < 5 /h in a non-supine position and a decrease of AHI more than 50% between supine and non-supine position[20]. Bignold et al. showed that position-dependent is defined as a total AHI ≥ 15/h, supine AHI as at least twice non-supine AHI and non-supine AHI < 15/h with ≥ 20 min of sleep in supine and non-supine sleep positions[21]. The new criteria, the Amsterdam Positional OSA Classification (APOC) introduced positional therapy and defined it as 1) AHI > 5/h, 2) > 10% of TST in both the best sleep position (BSP) and the worst sleep position, 3) BSP less than five, 4) lower OSA severity in BSP than total AHI or total AHI ≥ 40/h and a decreased AHI in BSP ≥ 25% compared to total AHI. No universal criteria exist for POSA in children[8]. A study by Verhelst et al. found that the prevalence of children with POSA and those with Down syndrome were 19% and 22.2%, respectively[6]. Previous studies reported that POSA among children with OSA and obesity were 30.3-58%[6-7]. Our data found 43.75% of POSA among children with obesity, which was not different from non-POSA children.

Previous studies examined the relationship between POSA and risk factors including age, obesity, tonsil size, and AHI. Zhang et al. reported that the left lateral decubitus AHI was significantly lower than supine AHI in children aged 6 to 13 years ($p < 0.05$)[22]. Cuhadaroglu et al. demonstrated that children with adenotonsillar hypertrophy had the highest AHI in the supine position ($p < 0.001$)[9].

A previous study by Verhelst et al. reported the association between POSA and age, obesity, tonsil size, AHI, supine AHI, and non-supine AHI[6]. In the study of Selvadurai et al., both significantly higher supine AHI and lower non-supine AHI were found in the POSA group, while the non-POSA group had a significantly lower mean SpO_2%[7]. Also, there was no association between POSA and non-POSA with a history of previous A&T[7]. In a recent study, children with POSA had a significantly higher supine AHI and a lower non-supine AHI; there were no significant differences in age, gender, or obesity in syndromic children[23]. Similar to our findings, no significant differences in age, gender, obesity, tonsil size and medical comorbidities were uncovered. Our study found that supine AHI and non-supine AHI were related to risk factors among children with POSA. Children with OSA worsened during REM sleep. However, time spent in a supine versus non-supine sleep position and REM versus non-REM sleep may be affected by both supine AHI and non-supine AHI. Verhelst et al. also reported that the supine AHI was higher than the non-supine position during REM sleep[6]. By contrast, Selvadurai et al. showed that supine AHI and non-AHI were no significantly different between children with POSA and those without POSA during REM sleep[7]. Previous research found that the severity of OSA had a significant difference in adults with POSA[24-25]. In contrast to our study, the severity of OSA was not significantly different in children with POSA.

Children with POSA are considered to benefit from positional therapy, which is an alternative treatment option. However, there is little data on the efficiency of positional therapy among children with OSA.

This study has several limitations. This is a retrospective study that used a small sample size and a single center. The majority of subjects were children who were overweight or obese and had a higher risk for OSA. The diagnosis of POSA is based on PSG that is considered for night-to-night variability in severity OSA and sleep position.

Conclusion

The prevalence of POSA among children with OSA was found to be 42%. Higher supine AHI and lower non-supine AHI were factors associated with POSA. Future studies should investigate the diagnosis criteria and anatomy collapsing in children with POSA for treatment beyond A&T.

Conflict of interest

The authors have no conflict of interest to declare.

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Results of Posteromedial Capsule and Superficial Medial Collateral Ligament Release on Gap and Alignment in Total Knee Arthroplasty for Varus Knee Deformity by Computer-Assisted Surgery Measurement

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Abstract

Objective: Soft tissue release and gap balancing in varus knee deformity following total knee arthroplasty (TKA) are important issues that lack conclusive results. Various techniques including posteromedial capsule (PMC) and superficial medial collateral ligament (sMCL) release have been used for varus knee correction and flexion gap balance.

Methods: We retrospectively reviewed data from patients who had undergone TKA with computer-assisted surgery measurement and the use of PMC and sMCL release by the preservation of anterior attachment of pes anserine at our institute from November 2015 to February 2016. Gaps and alignment were measured and recorded by computer-assisted surgery measurement.

Results: Twenty-one patients were enrolled. The mean age was 68.0 (48.0-78.0) years with a mean preoperative hip-knee-ankle angle of 8.1 (3.5-16.0) degrees and a mean flexion contracture (FC) of 11.3 (3.5-16.0) degrees. The mean corrections for varus deformity after PMC and sMCL release were 4.9 ± 2.8 and 3.4 ± 1.7 degrees, respectively, with the mean FC after PMC and sMCL release correction of 5.6 ± 3.5 and 1.3 ± 2.9 degrees. The mean medial extension gap changes after PMC and sMCL release were 1.8 ± 1.4 and 1.7 ± 1.0 millimetres, respectively, with mean medial flexion gap after PMC and sMCL release changes of 0.7 ± 0.9 and 5.1 ± 2.1 millimetres, respectively. There was no significant change in lateral gaps after PMC and sMCL release. No instability of the knee was found.

Conclusion: The sMCL released with the preservation of the anterior attachment of pes anserinus in total knee arthroplasty has an additional effect on varus knee correction and flexion gap balance after PMC release without the creation of knee instability.

Keywords: total knee arthroplasty, varus knee, computer-assisted surgery, superficial medial collateral ligament release, posteromedial capsule release

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ผลของระยะห่างและแนวของข้อเข่าเทียม จากการตัดเยื่อหุ้มข้อเข่าส่วนหลังด้านใน และการตัดส่วนตื้นของเอ็นยึดข้างข้อเข่าด้านใน ในการผ่าตัดเปลี่ยนข้อเข่าเทียมชนิดข้อเข่าโก่งออกด้านนอก โดยใช้คอมพิวเตอร์ช่วยในการผ่าตัดและวัดผล

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บทคัดย่อ

วัตถุประสงค์: การจัดสมดุลเนื้อเยื่อรอบข้อเข่าในการผ่าตัดเปลี่ยนข้อเข่าเทียม เป็นขั้นตอนที่มีความสำคัญ และในปัจจุบันยังไม่มีแนวทางปฏิบัติอย่างชัดเจน เทคนิคการผ่าตัดโดยการเลาะเนื้อเยื่อส่วนเยื่อหุ้มข้อเข่าส่วนหลังด้านใน (posteromedial capsule : PMC) และการเลาะส่วนตื้นของเอ็นยึดข้างข้อเข่าด้านใน (superficial medial collateral ligament : sMCL) ในการผ่าตัดเปลี่ยนข้อเข่าเทียมในผู้ป่วยที่มีเข่าโก่งออกด้านนอก (varus knee)

วิธีดำเนินการวิจัย: จากการศึกษาแบบย้อนหลังในผู้ป่วยที่ได้รับการผ่าตัดเปลี่ยนข้อเข่าเทียมโดยใช้คอมพิวเตอร์ช่วยในการผ่าตัดและวัดผลที่วชิรพยาบาลตั้งแต่ พฤศจิกายน 2558 ถึง กุมภาพันธ์ 2559 โดยใช้เทคนิคการตัดส่วนโดยการเลาะเนื้อเยื่อส่วนเยื่อหุ้มข้อเข่าส่วนหลังด้านในและการเลาะส่วนตื้นของเอ็นยึดข้างข้อเข่าด้านในโดยไม่เลาะส่วนกล้ามเนื้อเพส แอนเซอรีน (pes anserine) ออก ตามลำดับ

ผลการวิจัย: จากผู้ป่วยที่ได้รับการผ่าตัด 21 ราย พบว่า อายุเฉลี่ยของผู้ป่วยคือ 68.0 (48.0-78.0) ปี และค่าเฉลี่ยของมุมระหว่างสะโพก-เข่า-ข้อเท้า (hip-knee-ankle : HKA) เท่ากับ 8.1 (3.5-16.0) องศา โดยมีข้อเข่าติดในท่างอ (flexion contracture : FC) อยู่ที่ 11.3 (3.5-16.0) องศา ผลการของการผ่าตัดภายหลังการเลาะ PMC ส่งผลให้มุม HKA และ FC ลดลงเท่ากับ 4.9 ± 2.8 และ 3.4 ± 1.7 องศาตามลำดับ ผลของการผ่าตัดภายหลังการเลาะ sMCL ส่งผลให้มุม HKA และ FC ลดลงเท่ากับ 5.6 ± 3.5 และ 1.3 ± 2.9 องศาตามลำดับ ค่าเฉลี่ยของการเพิ่มระยะระหว่างข้อเข่าด้านใน ในท่าเหยียดภายหลังการเลาะ PMC และ sMCL เท่ากับ 1.8 ± 1.4 และ 1.7 ± 1.0 มิลลิเมตร สำหรับค่าเฉลี่ยของการเพิ่มระยะระหว่างข้อเข่าด้านใน ในท่างอ เท่ากับ 0.7 ± 0.9 และ 5.1 ± 2.1 มิลลิเมตร ไม่พบการเปลี่ยนแปลงของระยะระหว่างข้อเข่าด้านนอก และไม่พบภาวะเข่าไม่มั่นคงหลังการผ่าตัด

สรุป: ผลของการผ่าตัดเปลี่ยนข้อเข่าเทียม ชนิดพยาธิสภาพเข่าโก่งออกนอก โดยการเลาะส่วนตื้นของเอ็นยึดข้างข้อเข่าด้านในโดยไม่เลาะส่วนกล้ามเนื้อเพส แอนเซอรีน (pes anserine) ออก ภายหลังการเลาะเนื้อเยื่อส่วนเยื่อหุ้มข้อเข่าส่วนหลังด้านใน สามารถแก้ไขภาวะเข่าโก่งและจัดสมดุลของระยะข้อเข่าด้านในได้ดี โดยไม่ทำให้เกิดภาวะเข่าไม่มั่นคงหลังผ่าตัด

คำสำคัญ: การผ่าตัดเปลี่ยนข้อเข่าเทียม เข่าโก่งออกด้านนอก การผ่าตัดโดยใช้คอมพิวเตอร์ช่วยผ่าตัด การเลาะส่วนตื้นของเอ็นยึดข้างข้อเข่าด้านใน การเลาะเนื้อเยื่อส่วนเยื่อหุ้มข้อเข่าส่วนหลังด้านใน

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Introduction

Osteoarthritis (OA) of the knee is the most common articular disease, especially among the elderly population. In severe cases, it frequently causes pain and knee deformity, which worsens quality of life[1-3]. Total knee arthroplasty (TKA) is the treatment of choice in severe cases, which bypasses conservative treatment. Nowadays, the number of knee arthroplasty procedures has been increasing due to good clinical outcomes and patient satisfaction[4-6]. The goals of treatment in OA of the knee include restoring the axis of the knee by bone resection and gap balancing[7-11]. Varus deformity of the knee is a common pattern in OA. Soft tissue balancing by medial soft tissue release plays an important role in the correction of this type of deformity. Correction of varus deformity by the release of the superficial medial collateral ligament (sMCL) was suggested by Insall et al., but current reports have been varied and inconclusive[12-16]. From previous studies, the release of the posteromedial capsule (PMC) and sMCL showed additive effects on flexion and extension gaps in TKA[17-18]. Mullaji et al.[18] studied the effect of sequential release on fresh cadaveric knees using a CT-free computer navigation system. Data from the study showed severe instability of the knee after the release of sMCL. Therefore, it was suggested not to perform sMCL release except in the case of recalcitrant varus deformity.

Mihalko et al.[19] described the technique of sMCL release with preservation of pes anserine insertion by subperiosteal release from tibial insertion just medial to the pes anserine tendon and insertion to the medial aspect of the upper tibia extending 6 to 8 cm past the joint line. This is less extensive than the technique previously described by Insall[20] because it preserves the anterior attachment of pes anserine insertion, which plays an important role in knee stability. This modified Insall technique has become the main technique for sMCL release in our practice for more than 10 years.

The aim of this study was to analyse the amount of medial and lateral gap changes after the sequential release of PMC and sMCL using computer-assisted surgery (CAS) in patients who had undergone TKA. The gaps were measured before and after PMC and sMCL release using the modified Insall technique by the preservation of the anterior attachment of pes anserine. The hypothesis of this study is releasing sMCL after PMC release by using this technique will provide an additive effect on varus correction without the creation of instability.

Methods

After receiving approval from the Vajira Institutional Ethics Committee (study reference number 051/61), all procedures were performed in accordance with relevant guidelines. We retrospectively reviewed data from patients with primary OA of the knee who had undergone CAS TKA with a navigation system (Brainlab software knee 2.6) at our institution from November 2015 to February 2016. Inclusion criteria included patients aged 45-80 years diagnosed with primary OA of the knee through varus alignment (determined as hip-knee-ankle angle > 0 degrees) who had undergone unilateral TKA. Exclusion criteria included posttraumatic arthritis of the knee, inflammatory joint disease, revision surgery, and cases in which PMC or sMCL release was not performed. All patients underwent the same standard surgical procedure, as described below.

The Midvastus approach was done in all patients. After arthrotomy, as much osteophyte as possible was removed. Initial soft tissue release, just enough to move the tibia anteriorly, was done; the normal depth of release was about 2 to 3 centimetres below the joint line at the anterior part of the tibia extending to the equator of the tibia on the medial side. Subsequently, the CAS pins were inserted, and a CT-free navigation system was assembled. The proximal tibia was resected first using mechanical alignment, and a 220 Newton spring-loaded device (DePuy, Johnson and Johnson)

was inserted between the cut surface and distal femur for measuring gaps before and after each step of soft tissue release. An extension gap was defined as a gap between a proximal tibia cut and a distal femur in full extension. A flexion gap was defined as a gap between the posterior condyle of the femur and proximal tibia cut at 90 degrees of knee flexion.

PMC release was done by the release of the posteromedial corner and semimembranosus expansion (figure 1a-b). PMC release was not performed in a hyperextended knee or flexion contracture deformity below 5 degrees. sMCL was subperiosteally released, without pes anserine insertion detachment, after PMC release was done if varus deformity was more than 3 degrees using a bone chisel (figure 2a-b). We recorded all data at full extension, 30, 60, 90 and 120 degrees of flexion, respectively, after each soft tissue release step via Brainlab navigation system software 2.6 (figure 3a-d). After PMC and sMCL release, standard CAS TKA was continued. During the CAS procedure, after the trial TKA prosthesis was inserted, the stability of the knee was assessed. Intra-operative knee instability was identified as a gap change of more than 1 mm. after varus and valgus stress.

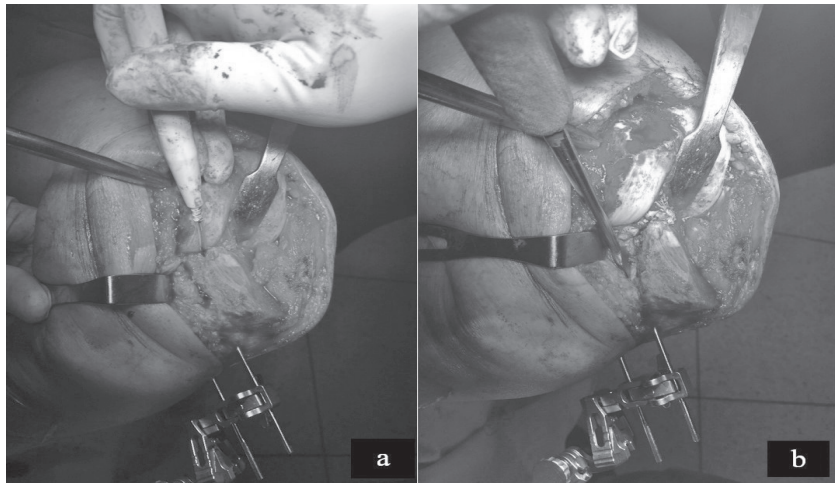

Figure 1a Initial posteromedial capsule release on the left knee using electrocauterisation
Figure 1b Posteromedial capsule release then release subperiosteally by a bone chisel

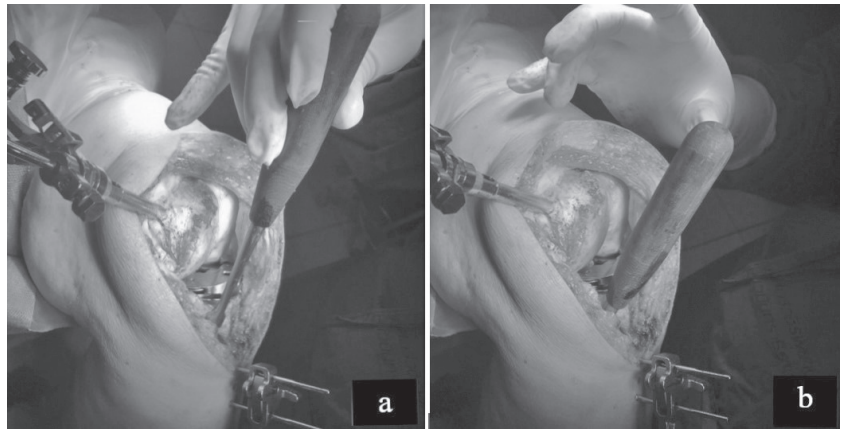

Figure 2a-b Superficial MCL of left knee was subperiosteally released downward to 8-10 cm. below joint line without pes anserine insertion detachment using bone chisel

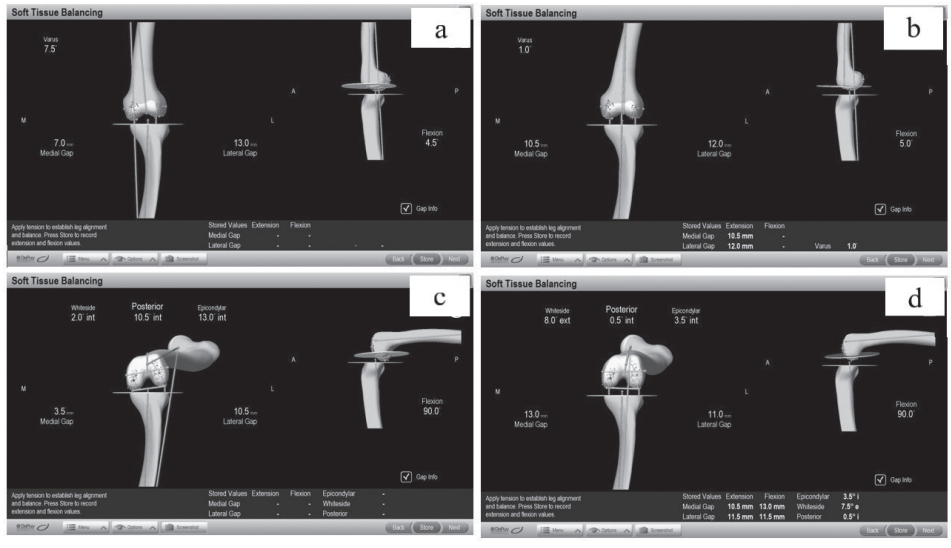

Figure 3a-d	CT-free navigation software showed how to measure alignment, extension and flexion gaps
Figure 3a	This figure shows medial and lateral extension gaps before PMC and sMCL release
Figure 3b	This figure shows medial and lateral extension gaps after PMC and sMCL release
Figure 3c	This figure shows medial and lateral flexion gaps before PMC and sMCL release
Figure 3d	This figure shows medial and lateral flexion gaps after PMC and sMCL release

Results

There were 21 patients (16 female and 5 male) with a mean age of 68.0 (48.0-78.0) years. The mean body mass index was 28.5 (20.7 – 39.9) kg/m^2. The mean preoperative hip-knee-ankle angle was 8.1 (3.5-16.0) degrees of varus with a mean flexion contracture of 11.3 (3.5-16.0) degrees. Sixteen knees were implanted with a fixed-bearing knee prosthesis, while the other five knees were implanted with a mobile-bearing knee prosthesis (table 1).

Table 1 Demographic data

			Range	SD
Gender	Female	16 (76.2%)		
	Male	5 (23.8%)		
Age (year)		68.0	48.0 – 78.0	9.0
BMI (kg/m^2)		28.5	20.7 – 40.0	5.0
Side	Right	13 (61.9%)		
	Left	8 (38.1%)		
Prosthesis	PFC Sigma	15 (71.4%)		
	Attune	1 (4.8%)		
	LCS	5 (23.8%)		
Comorbidity	Yes	11 (52.4%)		
	No	10 (47.6%)		
Preoperative HKA (degree)		8.1	3.5 - 16.0	3.4
Flexion Contracture (degree)		11.3	2.0 - 28.0	5.3

From the records, we performed PMC release in all patients and combined PMC and sMCL release in fourteen patients. The mean corrections of varus deformity after PM and sMCL release were 4.9 ± 2.8 and 3.4 ± 1.7 degrees, respectively, while the mean corrections of flexion contracture after PMC and sMCL release were 5.6 ± 3.5 and 1.3 ± 2.9 degrees, respectively, as shown in figure 4a-b.

The mean medial extension gap changes after PMC and sMCL release were 1.8 ± 1.4 and 1.7 ± 1.0 mm. respectively. The mean medial flexion gap changes after PMC and sMCL release were 0.7 ± 0.9 and 5.1 ± 2.1 mm., respectively (figure 5).

The mean lateral extension gaps after PMC and sMCL release were -1.3 ± 1.8 and -1.1 ± 1.6 mm., respectively. The mean lateral flexion gaps after PMC and sMCL release were -0.2 ± 1.0 and 0.1 ± 1.8 mm. (figure 5). No intra-operative instability was found. Postoperative varus and valgus stress tests were performed at full extension and 30-degree flexion. All patients' knees were stable and had no unstable feeling of the knee afterwards. The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

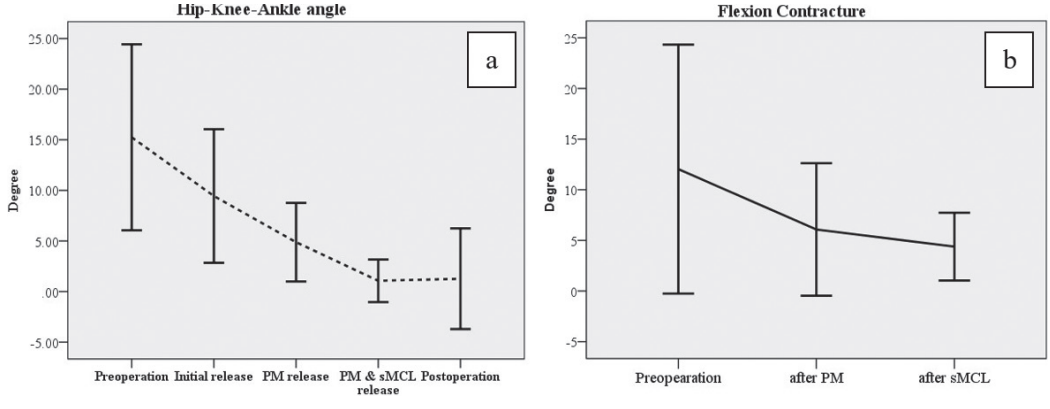

Figure 4a Hip-Knee-Ankle (HKA), Axis-X represents HKA and FC preoperative, after PMC and after sMCL release
Figure 4b Flexion contracture (FC) correction, Axis-Y shows HKA and FC (Degree), Positive HKA angle is defined as varus alignment

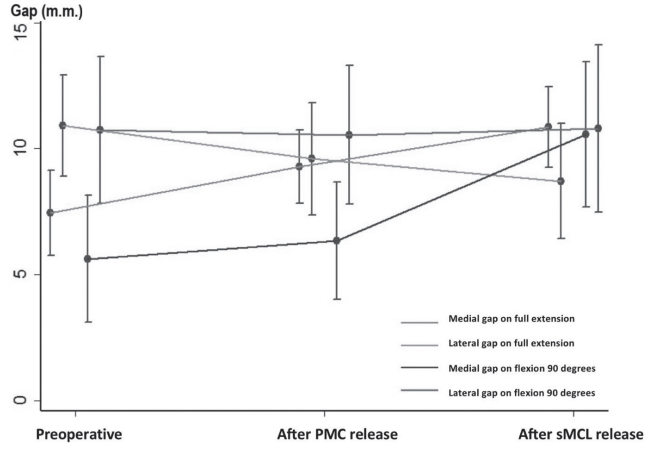

Figure 5 Medial and lateral gaps (mm.) changes at full extension and 90 degree flexion
Axis-X represents Medial and lateral gaps preoperative, after PMC and after sMCL release
Axis-Y shows Medial and lateral gaps (mm.)

Discussion

sMCL release had an effect on varus correction of both gaps with more effect on the flexion gap. The results also showed the negative effect of medial soft tissue release on the lateral gap. We believe that mechanical axis alignment restoration can explain this result.

Our results showed PMC release in total knee arthroplasty affected varus correction, including flexion contracture, similar to a previous study[17-19]. This technique had effects on both flexion and extension gaps with more effect on the extension gap.

Moreover, our results did not show instability after sMCL release, which was reported in the non-preserving insertion of the pes anserine sMCL release technique, pie-crusting or multiple needle puncturing techniques in previous studies[18, 21-23]. Differences in the results may have been caused by the surgical technique used in this study. Previously, the traditional technique had an over-correction effect on the flexion gap, while the modified technique in this study did not[24].

One of the main differences in the release technique was release without detachment of insertion of pes anserinus anteriorly; previous studies also showed the same results [25]. We believe that pes anserine provides dynamic stabilisation throughout the entire range of motion.

The strengths of this study included the use of CAS to record the changes in gaps among all patients, which provided minimal measurement error. Further, the results of PMC and sMCL release may be varied in long-term follow-up. Further study and long-term follow-up should be carried out.

This study had some limitations. First, a retrospective descriptive study was carried out with female predominance. Second, a small sample size was observed, but the changes in the gap were significant. Third, we used different types of prostheses.

Conclusion

The sMCL release with the preservation of anterior attachment of pes anserinus in TKA had an additional effect on varus knee correction after posteromedial capsule release without the creation of knee instability.

Conflict of interest

The authors declare no conflicts of interest in the completion of this study.

Acknowledgement

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Stress Shielding in the Proximal Tibia after Total Knee Arthroplasty: A Finite Element Analysis of 2- and 4-mm-thick Tibia Prosthesis Models

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Abstract

Objective: Proximal tibial bone resorption and osteolysis after total knee arthroplasty occur despite improved design and manufacturing processes. We utilized finite element analysis to study these phenomena.

Methods: We use SOLIDWORKS 2018 software to study stress and displacement of normal tibias and tibias implanted with a 4-mm-thick CoCr tibial tray (4mm-tray) or 2-mm-thick titanium alloy (2mm-tray). Under vertical loads of 1000 or 2000 N, the stress and displacement of both tibia tray models were analyzed. Stress on the supported proximal tibia 1 and 2 cm beneath the surface was analyzed and compared to stress in a normal tibia.

Results: Stress concentrated around the central region compared to the peripheral region in all models, which caused more deformation of the material in the central region. However, the 4mm-tray exhibited a more rigid construct compared to the 2mm-tray. Under any load, the 2mm-tray exhibited more tray deformation, with a central–peripheral deformation difference of approximately five times more than the deformation difference for the 4mm-tray. Moreover, stress on the peripheral region of the supported proximal tibia was only 18–22% of that of a normal bone for the 4mm-tray compared to 54–66% for the 2mm-tray.

Conclusion: Both tibial tray implant models exhibited some degree of stress shielding on the peripheral region of the supported proximal tibia. However, the greater modulus and thicker baseplate construct of the 4-mm CoCr tray exhibited a profound stress shielding effect. This stress shielding may correlate with a higher incidence of proximal tibia bone loss.

Keywords: finite element analysis, total knee arthroplasty, deformation of tibial tray, stress shielding

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การลดลงของความเครียดในกระดูกภายหลังการผ่าตัดเปลี่ยนข้อเข่าเทียม; การศึกษาโดยใช้ระเบียบวิธีไฟไนต์เอเลเมนต์ โดยใช้ข้อเข่าเทียมส่วนแผ่นทิเบียหนา 2 และ 4 มิลลิเมตร

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บทคัดย่อ

วัตถุประสงค์: ภาวะการณ์สลายและดูดซึมกลับของกระดูกทิเบียส่วนต้น (proximal tibial bone resorption and osteolysis) ภายหลังการผ่าตัดเปลี่ยนข้อเข่าเทียม เป็นผลมาจากการลดลงของความเครียดในกระดูก (stress shielding) โดยภาวะนี้ยังคงเกิดขึ้นแม้ว่าจะมีการพัฒนาเครื่องมือและกระบวนการผลิต ผู้ประพันธ์จึงนำโปรแกรมวิเคราะห์วิธีระเบียบวิธีไฟไนต์เอเลเมนต์ (finite element analysis; FEA) เพื่อทำการศึกษาถึงปรากฏการณ์ดังกล่าว

วิธีดำเนินการวิจัย: ผู้ประพันธ์ใช้โปรแกรม SOLIODWORKS 2018 ในการศึกษาภาวะเค้นและการกระจัดที่เกิดขึ้นทั้งในกระดูกทิเบียและข้อเข่าเทียมส่วนแผ่นทิเบีย (tibial tray) ชนิดโคบอลต์โครเมียมซึ่งมีความหนา 4 มิลลิเมตร และชนิดไทเทเนียมซึ่งมีความหนา 2 มิลลิเมตร ภายใต้แรงดันที่กระทำต่อแผ่นรองข้อเข่าเทียมซึ่งมีขนาด 1,000 และ 2,000 นิวตัน โดยวิเคราะห์การเปลี่ยนแปลงของความเค้นและการกระจัดของแผ่นรองข้อเข่าเทียมทั้งสองชนิด โดยวัดความเค้นที่ส่งผ่านไปยังกระดูกทิเบียที่ความลึก 1 และ 2 เซนติเมตร

ผลการวิจัย: ความเค้นที่เกิดขึ้นบริเวณศูนย์กลางเทียบกับบริเวณขอบ มีการเปลี่ยนรูปวัสดุของแผ่นรองมากในบริเวณศูนย์กลาง แต่อย่างไรก็ตาม แผ่นรองข้อเข่าเทียมชนิด 4 มิลลิเมตร แสดงถึงความมอดุลัสของสภาพยืดหยุ่น (Modulus of elasticity) มากกว่า และแผ่นรองข้อเข่าเทียมชนิด 2 มิลลิเมตร มีการเปลี่ยนรูปวัสดุมากกว่า โดยวัดความแตกต่างเปรียบเทียบระหว่างจุดศูนย์กลางและขอบของวัสดุมากกว่าอีกชนิดหนึ่งถึง 5 เท่า และความเค้นที่เกิดขึ้นผ่านแผ่นรองข้อเข่าเทียมชนิด 4 มิลลิเมตร ต่อกระดูกทิเบียที่บริเวณขอบเกิดขึ้นเพียงร้อยละ 18-22 เมื่อเทียบกับชนิด 2 มิลลิเมตร ซึ่งเกิดขึ้นถึงร้อยละ 54-66

สรุป: ข้อเข่าเทียมส่วนแผ่นทิเบียทั้งสองรูปแบบแสดงว่าให้เห็นว่ามีการลดลงของความเครียดในกระดูกของกระดูกที่บริเวณขอบของกระดูกทิเบีย อย่างไรก็ตามระดับความมอดุลัสของสภาพยืดหยุ่นและความหนาของแผ่นรองข้อเข่าเทียมชนิด 4 มิลลิเมตร แสดงให้เห็นภาวะส่งผลให้เกิดการลดลงของความเครียดในกระดูกที่มากกว่าอย่างมีนัยสำคัญ ซึ่งนำไปสู่การเกิดภาวะการณ์สลายและดูดซึมกลับของกระดูกทิเบียส่วนต้น

คำสำคัญ: การผ่าตัดเปลี่ยนข้อเข่าเทียม การลดลงของความเครียดในกระดูก ระเบียบวิธีไฟไนต์เอเลเมนต์ การเปลี่ยนแปลงรูปร่างของข้อเข่าเทียมส่วนแผ่นทิเบีย

วันที่รับบทความ 19 กันยายน 2565 **วันแก้ไขบทความ** 9 ธันวาคม 2565 **วันตอบรับบทความ** 13 ธันวาคม 2565

Introduction

The number of primary total knee arthroplasty (TKA) operations has increased markedly because of the aging society. Consequently, the number of revision TKA operations has also increased[1-2]. The major causes of TKA failure include infection, periprosthetic fractures, osteolysis, and aseptic loosening[1]. Despite advances in TKA technology, aseptic loosening and osteolysis are still major causes of revision[1,3]. In a retrospective study[4], medial proximal tibial bone loss after TKA was significantly higher in prostheses with thicker tibial baseplates compared with bone loss in prostheses with thinner tibial baseplates. These results correspond to recent reports[3,5-6] suggesting a high incidence of proximal tibial bone resorption for thick tibial baseplate designs. In our institute, we observed similar results with higher incidence of proximal tibial bone resorption in 4-mm-thick cobalt–chromium alloy (CoCr) tibial trays (figure 1) compared to 2-mm-thick titanium alloy (Ti) tibial trays. This may cause from differences between these two prostheses included the materials, designs, and tibial baseplate thicknesses. We hypothesized that these factors can change the pattern of deformation of the tibial tray under load, which may affect stress transfer to the supported proximal tibial bone.

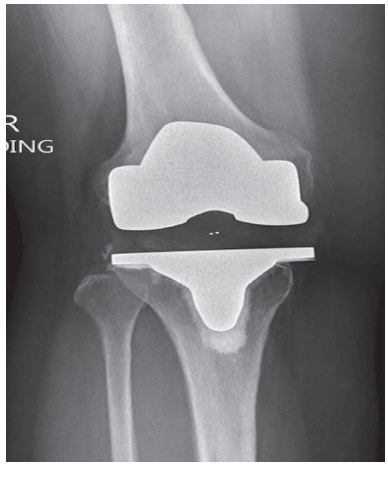

Figure 1 Plain radiograph of 72-year-old female shown bone resorption of proximal Tibia after total knee replacement with 4-mm-thick cobalt–chromium alloy for 5 years

Finite element analysis (FEA) is used to study patterns of load distribution, contact surface, and microdeformation of knee prostheses[7-9]. To understand proximal tibial bone resorption better, we used FEA to analyze the stress and deformation of different tibial trays and stress on the supported proximal tibia beneath the trays under load.

Methods

This research was approved by the Ethics Committee of Navamindradhiraj University (COE 07/2020). We used a computer-generated finite element (FE) model with SOLIDWORKS 2018 software to analyze stress and deformation of the normal tibia and two tibial models: a 4-mm-thick CoCr tibial tray (4mm-tray) and 2-mm-thick Ti tray (2mm-tray). The three-dimensional drawings of both tibial tray models are shown in Figure 2 from SOLIDWORKS 2018 software. The materials used for the tibial trays were as follows: cobalt–chromium alloy (ASTM F75 CoCr alloy) in the CoCr tray and titanium alloy (Ti–6Al–4V alloy) in the Ti tibial tray. The properties of the CoCr alloy and Ti trays are shown in Table 1. The material properties of each part of the tibia and bone cement from the previous work of Enab et al.[10] were used in the model, and they are shown in Table 2.

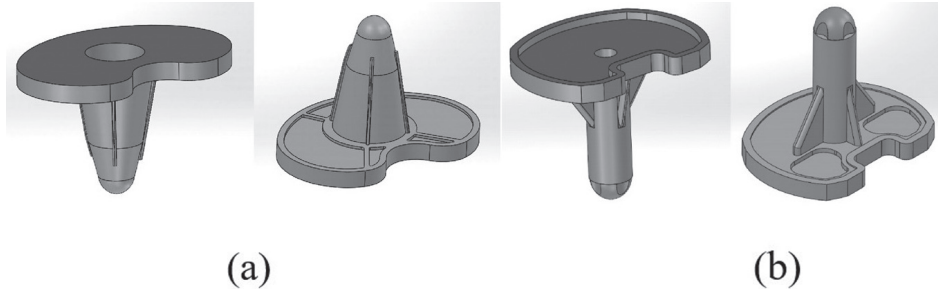

Figure 2 Three-dimension model of the tibial tray developed in FE simulation (a) Cobalt chromium alloy with 4 mm -thickness (b) Titanium based alloy (Ti-6Al-4V alloy) and Cobalt chromium alloy with 2 mm-thickness

Table 1 Material properties of alloy to be used in FE simulation

Properties	Material value		Units
	Ti-6A-4V alloy	ASTM F75 CoCr alloy	
Elastic Modulus	105	230	GPa
Poisson's Ratio	0.31	0.29	N/A
Mass Density	4430	8300	Kg/m^3
Tensile Strength	1050	480	MPa
Yield Strength	827	480	MPa
Thermal Expansion Coefficient	0.000009	12	/K
Thermal Conductivity	17	13	W/(m.K)

Table 2 Material properties represented in the FE model

Material	Modulus of elasticity (GPa)	Poisson's ratio
Cortical bone		
a. Top	14	0.3
b. Bottom	7	0.3
Cancellous bone		
a. Top	0.3	0.2
b. Top-middle	0.15	0.2
c. Middle	0.1	0.2
d. Bottom	0.05	0.2
PMMA cement	2.150	0.46

We matched the assigned tibial tray to the bone surface. A 2–3 mm layer of bone cement was created to simulate the cemented fixation of the tibial tray. The boundary conditions were set by clamping total support of the tibia tray and proximal tibial bone. Vertical loads of 1000 and 2000 N, which reflect the estimated normal and peak internal forces within the tibia during stance and the swing phase of subjects weighing 60 kg[11], were applied on the top surface of the tibial tray with equal force distribution on both sides of the plateau. The stress distribution of both tibia tray models was analyzed. Figure 3 showed examples of FE models under 1000N load. The stress on the supported proximal tibia at 1 and 2 cm beneath the surface was also analyzed for all models and compared to stress on the normal tibia and showed stress distribution on bone deep from surface 2 cm on FE models. We implemented a static analysis to calculate the stress distribution and deformation of the models. Central area deformation was determined at the closest part to the cone or stem in each design. Peripheral deformation is represented as a mean value of four measured points, as shown in Figure 4. Stress distribution on sagittal view of bone surface were shown in Figure 5.

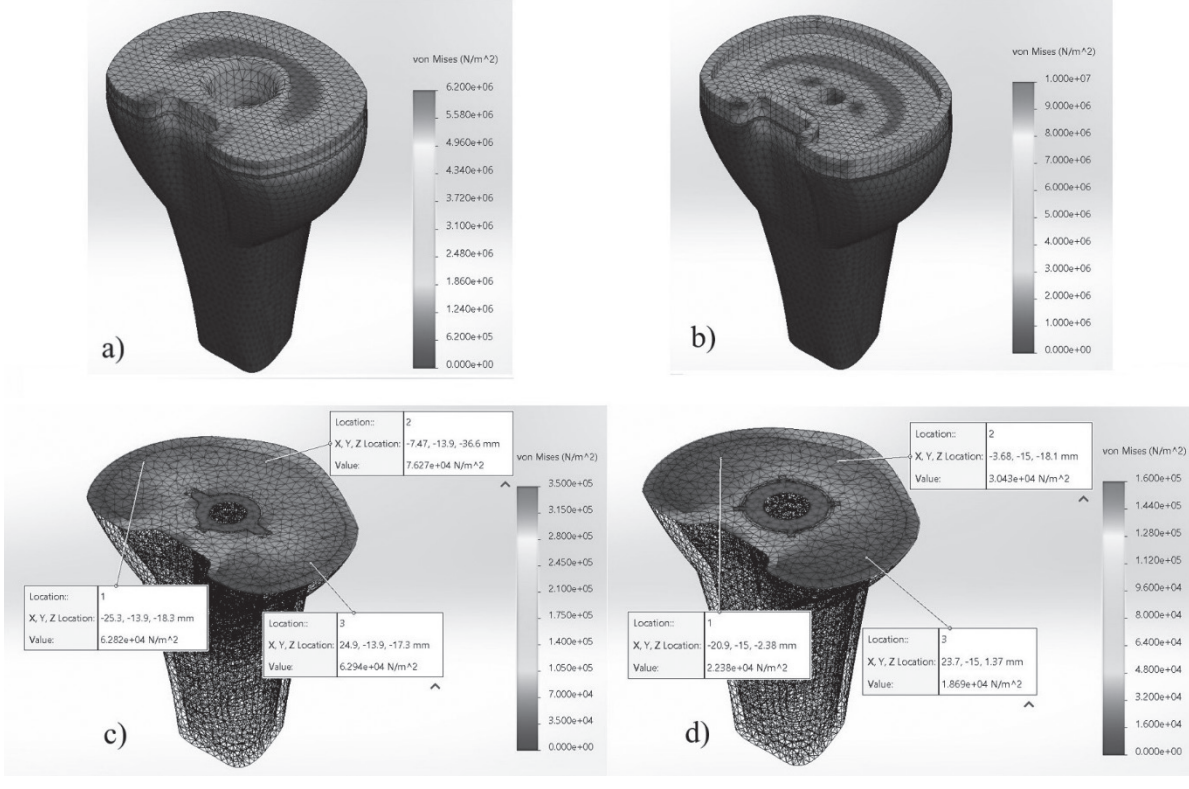

Figure 3 Stress distribution when force of 1000N applied to 4-mm CoCr based tibial trays (a) and 2-mm Ti based tibial tray (b) simulated using SOLIDWORKS. Stress distribution on bone deep from surface 2 cm of Peripheral area of 2-mm Ti based tibial tray (c) and 4-mm CoCr based tibial tray (d)

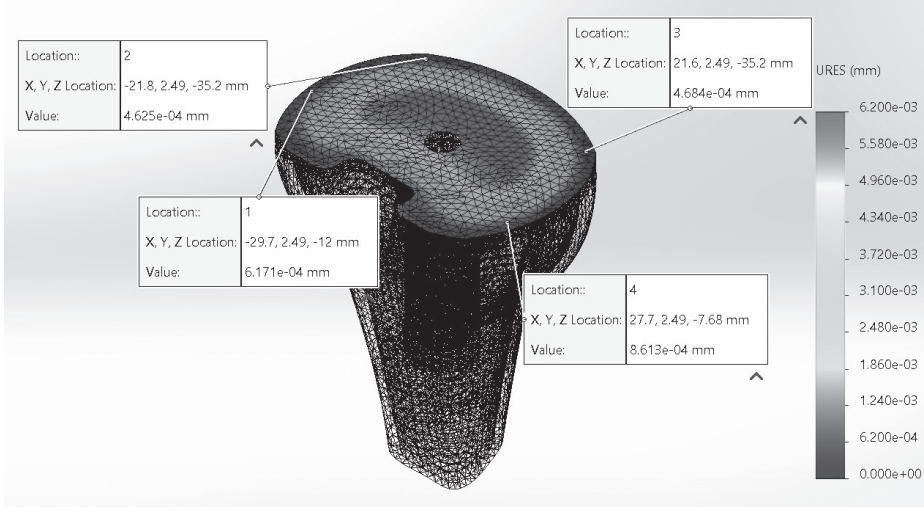

Figure 4 Displacement at 4 positions of Peripheral area of 2-mm Ti based tibial tray was measured after apply force of 1000 N

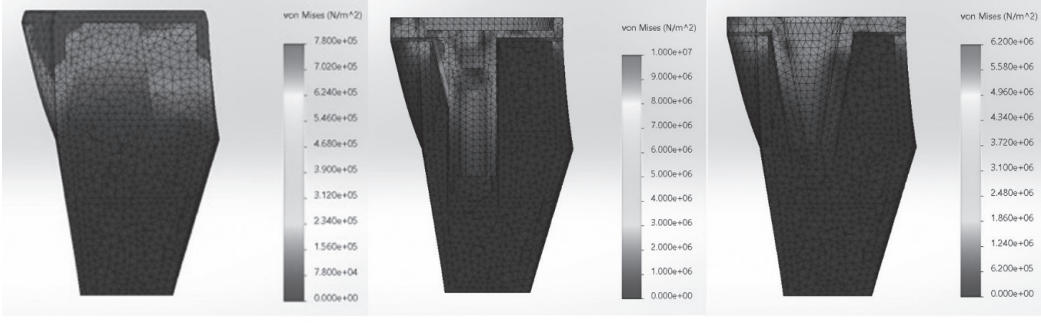

Figure 5 Sagittal view of stress distribution on normal bone (a), 2-mm Ti based tibial tray (b), and 4-mm CoCr based tibial tray (c)

Results

FE modeling revealed the same force patterns for the different tibial trays, with force concentrated more over the central region, as shown in Figure 2. When we increased force from 1000 to 2000 N, stress increased on the surface in both tibial tray models, as expected. Although the represented point may be slightly different between trays because of different designs, the pattern of stress concentration was the same, with more force concentrated over the central region for both tibial trays, as shown in Table 3.

Higher stress over the central region caused more deformation in the central region in both types of tibia trays, as shown in Figure 2. However, the degree of deformation was different. Under any load, the 4mm-tray showed less deformation compared to the 2mm-tray. Under a 1000 N load, the deformation difference between the central and peripheral regions for the 4-mm-tray was 13.05 microns and the difference for the 2mm-tray was 55.83 microns. The deformations of the trays under both loads are presented in Table 4.

Table 3 Stress on Ti Tibial tray and CoCr Tibial tray with force applied 1000 N and 2000 N (N/m^2)

	1000N		2000N	
	Peripheral	Central	Peripheral	Central
Ti Tibial tray 2 mm	2.78 MPa	10.10 MPa	5.50 MPa	20.19 MPa
CoCr Tibial tray 4 mm	2.33 MPa	6.22 MPa	4.71 MPa	12.11 MPa

Table 4 Detailed summary of deformation of tibia tray prosthesis under different load (Microns)

	Peripheral (micron)		Central (micron)		Peripheral-Central deformation (micron)	
	1,000 N	2,000 N	1,000 N	2,000 N	1,000 N	2,000 N
2 mm Ti tibial tray	6.02	13.36	61.85	123.90	55.83	110.54
4 mm CoCr tibial tray	6.275	14.08	19.33	38.50	13.055	24.42

Stress distribution underneath the tibial tray was also different between the two trays. At any load, the 4mm-tray had much less stress transfer to the peripheral part of the supported proximal tibia compared to the stress transfer for the 2mm-tray. Under a 1000 N load, stress on the peripheral region of the supported proximal tibia at 1 cm below the surface in a normal bone was 0.18 MPa. However, the stress values on the 4mm-tray and 2mm-tray were 0.04 and 0.12 MPa, respectively. If the load was increased to 2000 N, stress increased to 0.36 in a normal bone, 0.07 MPa in the 4mm-tray, and 0.23 MPa in the 2mm-tray. Load transfer to the supported proximal tibia was significantly reduced in both models but was more profound for the 4mm-tray. A detailed summary of stress underneath the tibial tray in all models is presented in Table 5.

Table 5 Detailed summary of stress underneath surface at different level with force of 1,000 N and 2,000 N (N/m^2)

	Normal Tibial bone (MPa)		2 mm Ti based tibial tray (MPa)		4 mm CoCr based tibial tray (MPa)	
	1,000 N	2,000 N	1000 N	2,000 N	1,000 N	2,000 N
Peripheral area at depth 1 cm	0.18	0.36	0.12	0.23	0.04	0.07
Peripheral area at depth 2 cm	0.11	0.21	0.06	0.13	0.02	0.05
Central area at depth 1 cm	0.13	0.27	0.05	0.1	0.03	0.06
Central area at depth 2 cm	0.06	0.12	0.09	0.18	0.03	0.06

Discussion

Loosening of the tibia prosthesis after TKA is one of the unsolved problems in knee arthroplasty. Many hypotheses explain early loosening, including inadequate fixation, poor cement technique, stress shielding, or implant malposition[6, 12]. Implant design, such as a cement pocket under the tibial tray and the roughness of the surface, are possible causes leading to the modification of the design. Despite improvements in the design, tibial loosening is still widely reported[6,12-13]. Proximal tibia resorption after TKA may aggravate this problem. A higher incidence of proximal tibial resorption in thicker tibial tray designs was reported, which aligned with our unreported data. When comparing the 4-mm-thick CoCr tray to the 2-mm-thick Ti tray, we found four main differences: 1) bearing mobility, which can be fixed or mobile, 2) tray design, 3) material, and 4) tray thickness. The 4-mm-thick CoCr trays used at our institution are mobile-bearing tibial trays, whereas the 2-mm-thick Ti trays are fixed-bearing tibial trays. The mobile-bearing knee has theoretical advantages, including less volume of wear particle creation from lower contact stress, which should lessen the wear particle-related problems. However, more recent reports showed that the amount and size of wear particles were similar in both mobile-bearing and fixed-bearing designs[14-15]. No clinical results suggest differently[3,6,13,16]. Therefore, we excluded the possibility of wear particle-related causes for proximal tibia bone loss or early loosening. Thus, these phenomena can be explained by the differences in the material, design, or thickness of tibial baseplates. Hence, the thickness of the tibial tray and a higher Young's modulus material may explain the differences, leading to the present study.

Our results showed the same pattern of stress and deformation for both tibial tray models. Stress was more concentrated around the central region of the trays, resulting in more deformation in the central region in both models. However, the degree of deformation was much lower in the 4mm-tray model. When we analyzed stress on the supported proximal tibia for the normal tibia and post-TKA models, we found that less stress was transferred to the supported proximal tibia in the post-TKA models, suggesting a stress shielding pattern. However, the stress transfer was much less in the 4mm-tray model, indicating a profound pattern of stress shielding. These results may be explained by the higher modulus material combined with the thicker construct in the 4mm-tray model. According to Wolff's law, stress shielding will result in some degree of bone loss, which may occur in the supported proximal tibia in our model.

In addition to the material and thickness, the design of the tibial tray may affect stress shielding. Two prosthesises built with almost equal thicknesses and the same material were shown to induce significantly different rates of proximal bone resorption[17]. The 2mm-tray in our study was designed with a reinforced peripheral ring, which theoretically improves the stiffness of the peripheral region compared to the 4mm-tray. However, the overall effects of the material and thickness overcome the effect of the design in our study.

There are several limitations to our study. Our study shows FEA results only; clinical application in a real situation depends on each surgeon. The load applied to the tibia in our study was in one direction. However, the normal knee is subjected to rotational force also, which was not applied in our FEA model. Further studies with more variables may show different results.

Conclusion

Because 4-mm-thick CoCr trays were made with a stronger material and thicker baseplate, the degree of deformation under load was less compared with the deformation in the 2-mm-thick Ti tibial tray. The FEA model also demonstrated

that less stress was transferred to the supported proximal tibia underneath the tray, which may correlate with the resorption of bone in this region. Further studies with different tibial tray models or more complex load patterns can help us understand the complex nature of failure in knee arthroplasty.

Conflict of Interest

We declare no conflict of interest in this study.

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Clinical Methicillin-Resistant *Staphylococcus aureus* May Transfer from Hospital to the Community Through Foods

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Abstract

Objective: To investigate the capability of methicillin-resistant *Staphylococcus aureus* (MRSA) and *mecA*-carrying *Staphylococcus aureus* (MCSA) transfer from hospital to community through foods due to the *mecA* gene is responsible for various antimicrobials resistance.

Methods: We investigated four MRSA from patients and healthy carriers and one *mecA*-carrying *S. aureus* (MCSA) from food, whether they were capable of surviving through acidic condition and simulated gastrointestinal system. All bacterial strains were examined in green papaya salad's liquid portion (GPL), pH 2.0 and pH 3.0 to test their toleration ability in acidic food. Bacterial toleration to gastrointestinal system was investigated using 0.3% (w/v) pepsin-supplemented phosphate buffer saline (PBS) (pH 2.0 and pH 3.0), and different concentrations bile salt-supplemented tryptic soy broth (TSB). T-test was used to compare the bacterial survival rates at room temperature and 4ºC, before exposure to GPL, pH 2.0 and pH 3.0.

Results: The results revealed that MRSA and MCSA could tolerate in GPL, pH 3.0 and pH 2.0 for 2 h and 1 h, respectively. Bacterial exposure to 4ºC for 3 h before incubated in GPL, pH 2.0, significantly prolonged bacterial survival ($P < 0.05$). Toleration to simulated gastrointestinal system demonstrated that clinical MRSA strain PSU20 well tolerated to simulated gastric juice, pH 3.0 [0.3% (w/v) pepsin] for at least 1 h with the bacterial survival populations of 4.40 log CFU/ml. In addition, this PSU20 well tolerated to all concentrations of bile salts.

Conclusion: This study suggests that clinical MRSA has potential to transfer from hospital to community through foods and is able to break the gastrointestinal innate immunity establishing infection in human. This is crucial for public health stand point.

Keywords: MRSA, hospital, gastrointestinal tract, *mecA*, bile salt

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาความสามารถของ methicillin-resistant *Staphylococcus aureus* (MRSA) และ *mecA*-carrying *Staphylococcus aureus* (MCSA) ในการถ่ายทอดจากโรงพยาบาลไปยังชุมชนผ่านทางอาหารเนื่องจากยีน *mecA* ก่อให้เกิดการดื้อยาต้านจุลชีพอย่างหลากหลาย

วิธีดำเนินการวิจัย: การศึกษาทำเพื่อตรวจสอบความสามารถของ MRSA และ MCSA ว่ามีความสามารถรอดชีวิตในอาหารที่เป็นกรดและในสภาวะระบบทางเดินอาหารเทียมที่สร้างขึ้นได้หรือไม่ แบคทีเรียทั้ง 5 สายพันธุ์ ได้รับการทดสอบความทนกรดใน green papaya salad's liquid portion (GPL) ที่ pH 2.0 และ 3.0 ส่วนความทนทานต่อสภาวะในระบบทางเดินอาหาร ทดสอบโดยการใช้ phosphate buffer saline (PBS) ที่มี pepsin ความเข้มข้นร้อยละ 0.3 (w/v) (pH 2.0 and pH 3.0) และใช้ tryptic soy broth (TSB) ที่มี bile salt ความเข้มข้นต่าง ๆ ส่วนการรอดชีวิตของแบคทีเรียใน GPL pH 2.0 และ 3.0 ที่อุณหภูมิห้องเมื่อเปรียบเทียบกับที่ 4°C ได้รับการวิเคราะห์ทางสถิติโดยวิธี T-test

ผลการวิจัย: ผลการทดลองแสดงให้เห็นว่า MRSA และ MCSA สามารถทนทานสภาวะความเป็นกรดของ GPL pH 3.0 และ 2.0 ได้เป็นเวลา 2 ชั่วโมง และ 1 ชั่วโมง ตามลำดับ การให้แบคทีเรียสัมผัสอุณหภูมิต่ำที่ 4°C เป็นเวลา 3 ชั่วโมงก่อนทดสอบความเป็นกรดใน GPL pH 2.0 พบว่าสามารถทำให้แบคทีเรียมีการรอดชีวิตได้ยาวนานขึ้นอย่างมีนัยสำคัญทางสถิติ ($P < 0.05$) การทดสอบความทนทานต่อสภาวะในระบบทางเดินอาหาร พบว่า MRSA สายพันธุ์ PSU20 ที่แยกได้จากผู้ป่วยในโรงพยาบาล สามารถทนต่อน้ำย่อยกระเพาะอาหารสังเคราะห์ที่ pH 3.0 ได้อย่างน้อย 1 ชั่วโมงโดยที่ยังสามารถคงปริมาณเชื้อรอดชีวิตได้ถึง 4.40 log CFU/ml นอกจากนี้ สายพันธุ์ PSU20 ยังทนต่อ bile salt ในทุก ๆ ความเข้มข้นที่ทดสอบอีกด้วย

สรุป: การศึกษานี้แสดงให้เห็นว่า MRSA จากโรงพยาบาล มีความสามารถในการถูกถ่ายทอดไปสู่ชุมชนได้ผ่านทางอาหารและสามารถผ่านระบบภูมิคุ้มกันชนิด innate immunity ในระบบทางเดินอาหารและอาจก่อโรคได้ในมนุษย์ ซึ่งสิ่งเหล่านี้ส่งผลต่อระบบสาธารณสุขโดยรวม

คำสำคัญ: MRSA โรงพยาบาล ระบบทางเดินอาหาร *mecA* เกลือน้ำดี

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Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a nosocomial pathogen that was observed in the last quarter of 1960[1]. It is frequently found to be the crucial causative agent of human skin abscesses. Phenotypic characteristic of methicillin resistance is contributed by the presence of *mecA* gene coding for penicillin-binding protein2a (PBP2a), responsible for low β-lactam antibiotic affinity[2]. It can cause a wide range of severity upon human infections and its incidence is increasingly reported in hospitals worldwide. In United States, 2003, approximately 400,000 inpatients were reported to be infected by MRSA[3]. In addition, in 2005, the causation of approximately 19,000 hospital deaths in United States was resulted from MRSA infections[4].

Despite that MRSA is able to cause nosocomial infections, the potential MRSA strains carrying important virulence factors are also reported from foods[5-7]. Recent report has described the role of MRSA in acute gastroenteritis outbreaks acquired from the community[8]. The report described the link between the infection of staphylococcal enterotoxin C (SEC)-producing MRSA and the consumption of food from a delicatessen by pulsed-field gel electrophoresis (PFGE). This outbreak was subsequently found to clearly show that foods can act as the important MRSA vehicles.

Our previous report has pointed the high degrees of MRSA and *mecA*-carrying *S. aureus* (MCSA) contamination rates in the ready-to-eat foods sold in the hospital area. MRSA and MCSA strains from the foods and clinical sources were also genetically compared and showed high degrees of genetic similarity[6]. In addition, MCSA strains were found to survive in acidic food such as a green papaya salad (GP) which is consumed worldwide. Therefore, this study aims to investigate the survival capability of MRSA and MCSA strains in acidic food and simulated gastrointestinal system. This may help understanding the transfer of pathogens from hospital to community.

Methods

Bacterial strains

Four important MRSA strains and one MCSA strain isolated from patient, healthy carriers, and ready-to-eat foods, were collected from our previous studies[6,23] using Baird Parker agar, and selected as the surrogates in this study. Characteristics of bacterial strains were described in Table 1.

Survival of MRSA and MCSA in acidic food

Due to in our previous study, MRSA was found in GP in high rate, thus GP was employed as a model to investigate the acid toleration of MRSA and MCSA. Briefly, GP samples were purchased and 99 ml of the green papaya salad's liquid portion (GPL) was separated and kept into the glass bottle (Duran, Germany). The pH of GPL was adjusted to be 3.0 and 2.0 using 1.0 M citric acid (Sigma-Aldrich, USA). Afterwards, GPL were sterilized by autoclave. Tested bacteria were prepared as previously describe[6]. In brief,

Table 1 Characteristics of 4 MRSA strains and a MCSA strain used in this study

Strain	Date of isolation	Virulence genes							Source of isolation	Enterotoxin genes	Reference
		mecA	*luk-PV*	*vWbp*	*spa*	*coa*	*femB*	*sea*			
PSU20	24 Jan 2011	+	-	-	+	+	+	+	Hospital patient	*seg*, *sei*	23
PSU24	25 Jan 2011	+	-	-	-	-	-	-	Healthy carrier	*seg*	23
PSU83	25 Jan 2011	+	-	-	-	-	-	-	Healthy carrier	-	23
[a]PSU109	9 Sep 2013	+	-	-	+	-	-	-	Seasoned rice	*sec*, *sed*	6
PSU172	12 Dec 2013	+	-	-	-	-	-	-	Seasoned rice	-	6

[a]PSU109 carried *mecA* gene but was susceptible to cefoxitin by disk diffusion method, classifying as a MCSA strain.

an individual colony was grown in 5 ml of tryptic soy broth (TSB) at 37°C for 6 h with aeration at 150 rpm. Bacterial cells were washed using 0.85% NaCl solution (NSS) and adjusted to be 0.5 McFarland turbidity standards (approximately 1.5×10^8 cfu/ml) in NSS by Densitometer (Biosan, Latvia). Ten-fold dilution was performed to obtain a working culture (1.5×10^7 cfu/ml) using NSS as the diluent. One milliliter of a working culture was spiked into a 99 ml of GPL, pH 3.0 or pH 2.0, thoroughly mixed, and incubated statically at room temperature for 6 h. Survival of bacteria was monitored at 7 time points (0 to 6 h) by surface plate count on mannitol salt agar (MSA). The experiment was performed in triplicate. Moreover, to test that the cold exposure to bacteria can increase bacterial survival, the effect of cold temperature was also investigated using the same protocols as described above except that a working culture was kept at 4°C for 3 h before adding to GPL, pH 3.0 or pH 2.0.

Survival of MRSA and MCSA in simulated gastric juice

To simulate the condition of gastric system, phosphate buffer saline (PBS), pH 2.0 and pH 3.0, supplemented with 0.3% (w/v) pepsin (Sigma-Aldrich, USA) were used. The experiment was carried out as described by Wang et al[9] with slight modifications. Briefly, a 1 ml of 1.5×10^6 cfu/ml bacterial culture was added into 9 ml of 0.3% (w/v) pepsin-supplemented PBS (pH 2.0 and pH 3.0) and incubated at 37°C for 1 h. Bacterial survival was assessed by surface plate count on MSA. A 0.3% (w/v) pepsin-supplemented PBS, pH 6.2 was used as a control. The experiment was performed in triplicate.

Survival of MRSA and MCSA in bile salt

To simulate the condition of human intestinal tract, bacteria were tested for their toleration in various concentrations of bile salts. The experiment was performed as previously described[10] with slight modifications. In short, a working bacterial culture of 1.5×10^7 cfu/ml was prepared as described above. One milliliter of working culture was spiked into a 99 ml of sterile TSB supplemented with 0.1%, 0.3%, and 0.5% (w/v) of bile salt (Sigma-Aldrich, USA) and incubated statically at 37°C for 4 time points, 0 min, 30 min, 60 min, and 90 min. Bacterial survival was assessed by surface plate count on MSA. Sterile TSB was used as a control. The experiment was performed in triplicate.

Statistical analysis

Data were analyzed using SPSS for Windows software, version 11.0 (SPSS, Chicago, IL). T-test was used to compare the survival rates among bacteria at room temperature and at 4°C, before exposure to GPL, pH 3.0 and pH 2.0. Level of significance was set as $P < 0.05$.

Results

Survival of MRSA and MCSA in GPL

Due to the previous study has shown that MRSA and MCSA strains could well tolerate to GP, pH 4.0[6]. Thus, in this study, GPL was also employed as a model to assess the acid toleration capability of bacteria. At pH 3.0, the results revealed that PSU24 isolated from the throat of a healthy carrier, could withstand this degree of acidity for 3 h with the survival population of 3.16 log CFU/ml (mean value). However, it was at the undetectable limit after 4 h of incubation (figure 1). PSU20 isolated from hospital patient was also able to tolerate with the survival populations at 2 h of 3.11 log CFU/ml. All strains were not detected after 4 h.

The incubation of bacterial culture at 4°C before exposing them to the acidic pH in this current study was carried out since some raw materials are stored at low temperature. Bacterial survival ability at 4°C (pH 3.0) prolonged the bacterial survival time. PSU24 could survive for longer until 4 h with bacterial survival of 2.09 log CFU/ml, compared to the condition at room temperature which was under detection limit. Similar fashion was found in PSU20 and PSU83 (Figure 1). At 4°C (pH 2.0), it was found that cold temperature was capable of elevating the survival rates. At 0 h of incubation, we found the bacterial

population around 3.14 to 3.68 log CFU/ml in all strains. PSU24 also exhibited the highest rate of acid toleration expressing 2.48 log CFU/ml at 3 h of incubation. Furthermore, all strains could survive longer than those stored at room temperature with undetectable limit since 2 h of incubation (figure 1).

Survival of MRSA and MCSA in simulated gastric juice

Low pH of gastric system plays an important role as an innate immunity to destroy pathogens. The results in this experiment showed that MRSA strains from healthy carriers and foods could not tolerate to the simulated gastric juice, pH3.0 and pH 2.0, with 0.3% (w/v) of pepsin supplemented. They were under undetectable limit at 1 h of incubation. However, clinical MRSA strain PSU20 demonstrated a relatively strong toleration to simulated gastric juice, at pH 3.0 with the bacterial survival populations of 4.40 log CFU/ml after 1 h of incubation (figure 2). This may pose the health risk to the humans with its ability to break through an important innate immunity because PSU20 is a Staphylococcal enterotoxin-producing MRSA.

Survival of MRSA and MCSA in bile salt

Bile salts are antibacterial compounds that play the important roles in disruption of several bacterial components, e.g., destroying bacterial cytoplasmic membrane, denaturing proteins, and causing oxidative damage to bacterial DNA[11]. Therefore, we assessed the degree of bile tolerance in MRSA and MCSA in this current study. At 0% bile salt, the well-growth of all strains was

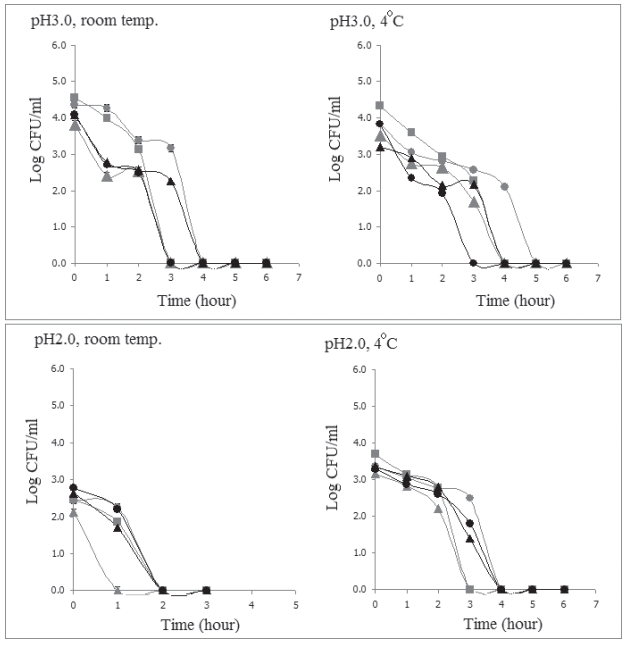

Figure 1 Survival of 4 MRSA strains and a MCSA in 4 storage conditions of GPL, storage at room temperature and expose at pH 3.0, storage at 4°C before storage at pH 3.0, storage at room temperature and expose at pH 2.0, and storage at 4°C before storage at pH 2.0. (■) PSU20. (●) PSU24, (▲) PSU83, (●) PSU109, (▲) PSU172

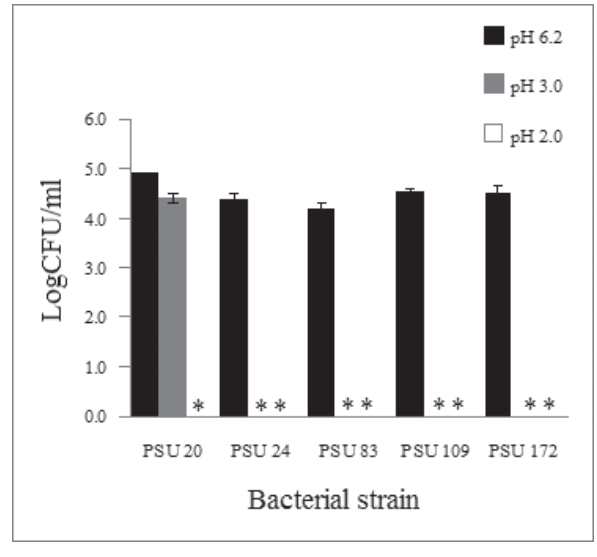

Figure 2 Survival of 4 MRSA strains and a MCSA in the simulated gastric juice (0.3% pepsin), pH 2.0 and pH 3.0 for 1 h of incubation at 37°C. Simulated gastric system (0.3% pepsin), pH 6.2 was used as a control. Asterisk (*) represents the lack of bacterial survivors

observed at 90 min of incubation (figure 3). However, at 0.1% bile salt, PSU172 gradually decreased and exhibited its final bacterial population at 90 min of 2.68 log CFU/ml (Table 3). In addition, this PSU172 was undetectable at 60 min in 0.3% and 0.5% bile salt conditions. Clinical MRSA strain PSU20 was considered unaffected by bile salt throughout the experiment. This suggests that clinical MRSA strains PSU20 from a patient is possible to survive human intestine.

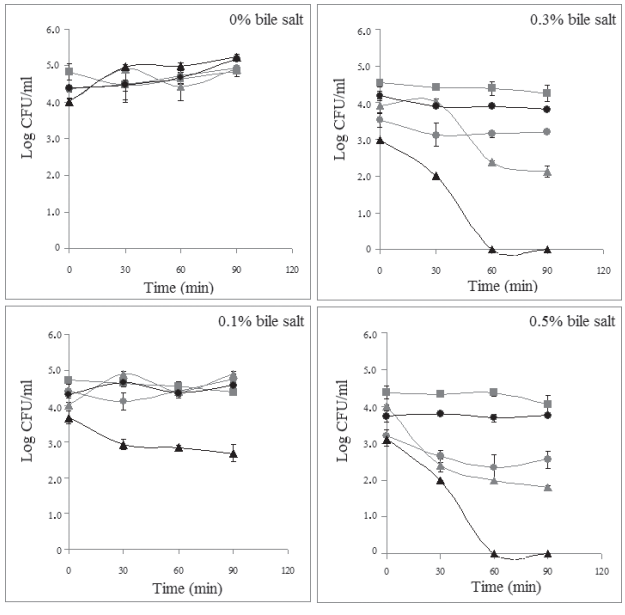

Figure 3 Survival of 4 MRSA strains and a MCSA in TSB supplemented with various concentration of bile salts (0.1%, 0.3%, and 0.5%). (■) PSU20. (●) PSU24, (▲) PSU83, (●) PSU109, (▲) PSU172

Discussion

In this current study, it was found that the bacteria that were exposed to low temperature were tougher in acid toleration than unexposed. There were some reasons that have previously been described. Anderson et al[12] investigated the induction of cold shock responses in *S. aureus* strain UAMS-1. It was grown at 37°C to the mid-log phase before incubated at 10°C for 30 min. It was shown that 46 genes were upregulated. Moreover, genes involved with anti-programmed cell death, *irgA*, *irgB* and several virulence genes were also induced. Cold shock gene, *cspB* (*csp* stands for cold shock protein) was induced 9.3 folds compared to the uninduced condition. Also, *cspA* was upregulated for 2 folds. This *cspA* was found to share the homology with other bacterial species and was shown to act as RNA chaperones to prevent RNA secondary structures, allowing the RNA to smoothly perform its biological roles in the bacterial cells[13]. Raju et al[14] also demonstrated that a stepwise adaptation of methicillin-susceptible *S. aureus* to oxacillin produced the greater resistance to lactic acid and citric acid, facilitating the survival of bacteria in gastric juice. It was thought that in the person who received antimicrobial agent whose mechanism of action was similar to or involved with oxacillin for treatment of infections (e.g. dicloxacillin), may be at higher risk in infection through consumption of acidic food contaminating MRSA or MCSA strains.

Although the favorable pH required for the growth of *S. aureus* was reported to be the range of 4.5-9.3[15], MRSA and MCSA strains in this present study were shown to be much higher tolerated to acidic pH and these bacterial species were also found in GP in high rates[6]. This result infers that MRSA and MCSA are able to retain their high number for at least 6 h at pH 4.0 (general pH level in GP) and can survive until they reach the human gastrointestinal tract. The acid toleration of *S. aureus* is not frequently reported. Most of *S. aureus* strains were reported to be suppressed in acidic condition. Abu-Ghaza et al[16] showed that 0.03% citric acid significantly inhibited clinical *S. aureus* growth. In addition, in one study, citric acid was shown to act as an effective permeabilizer killing Vancomycin Intermediate *S. aureus* (VISA) and MRSA isolated from orthopedics surgical site of infection[17]. Furthermore, one report from Nagoba et al[18] demonstrated the employment of 3% citric acid gel in the treatment of diabetic foot ulcers with *S. aureus* infections and this concentration of citric acid was effective in control of foot infection with the success rate more than 94% for Wagner grade I and II ulceration. These studies suggest that clinical *S. aureus* is sensitive to citric acid, which was opposite to our study that showed that a clinical MRSA was resistant to citric acid. Collectively, the finding that MRSA and MCSA in this current study tolerates to acidic condition results in the conclusion that GP can also be a potential vehicle of food-borne MRSA infections.

Lactic acid bacteria with the potential to be the probiotic bacteria can tolerate gastric juice in high rate[19] but for other group of bacteria it seems to possess the less ability in such a stringent condition. In Gram-negative bacteria, Zhu et al[20] demonstrated that the clinical *E. coli* strain 690 and *Helicobacter pylori* strain E5 were more susceptible to acidic condition with 1 mg Pepsin more than the control (without Pepsin). The toleration of simulated gastric juice of PSU20 in this experiment was thought to be crucial because it has high possibility to make an establishment of infection to the intestine. Furthermore, this PSU20 contains Staphylococcal enterotoxin G and Staphylococcal enterotoxin I genes (table 1), which is able to cause Staphylococcus food poisoning. These enterotoxins are found to be heat stable and resisted from proteolytic enzyme destruction such as pepsin, trypsin and also can keep their toxic activity[21].

Bile salt is secreted from the liver and acts as an innate defense mechanism of intestine[22]. Although *S. aureus*, a Gram-positive bacterium, is thought to be sensitive to bile salt, its resistant phenotype can be frequently observed. Recently, the work from Sannasiddappa et al[22] has uncovered the underlying mechanism by which *S. aureus* was able to tolerate to bile salts. The *mnhF* gene is found to confer such a tolerance by coding MnhF protein, a Na^+/H^+ antiporter subunit F1 responsible for sodium ion and proton ion secretions as well as bile salt efflux. The *mnhF* gene is in a *mnhABCDEFG* operon but only *mnhF* alone was shown to be enough to confer bile salt tolerance. We accessed the data in the National Center for Biotechnology Information (NCBI) and used the *mnhF* nucleotide sequence (294 nucleotides) for searching and found that *mnhF* gene was present in a wide variety of *S. aureus* and MRSA strains, for instance, MRSA strain DAR4145, MRSA USA300 (data not shown). These sequences exhibited 100% identity. Thus, it has a possibility that *mnhF* may equipped in MRSA strains in this present study and play a role in bile salt tolerance.

Conclusion

Although previous reports have frequently described the susceptibility of *S. aureus* including MRSA to organic acids including citric acid, MRSA and MCSA in this current study exhibited certain degrees of acid tolerance. More importantly, a clinical MRSA strain PSU20 from hospital could also survive in gastrointestinal system in high numbers. The MRSA equipped with Staphylococcal enterotoxins and other virulence factors including antimicrobial resistance, can lead to severe illnesses and can prolong the hospital stay. Thus, this study demonstrates the existence of a pathogenic MRSA strains that has potential to transfer from hospital to human through foods. This is crucial to the public health standpoint.

Conflicts of interest

The authors declare no conflicts of interest in this study.

Acknowledgement

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Spironolactone to Prevent the Progression of Vascular Calcification among Peritoneal Dialysis Patients: A Pilot Randomised Controlled Trial (SV-CAPD trial)

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Abstract

Objective: The purpose of the study was to investigate the efficacy and safety of spironolactone to prevent vascular calcification among peritoneal dialysis patients.

Methods: This study was a randomised, double-blinded placebo-controlled trial conducted from August 2018 to December 2020 at Vajira Hospital, Thailand. We randomly assigned peritoneal dialysis patients to receive either 25 mg of spironolactone daily or a placebo for 6 months. Coronary artery calcium scores and laboratory tests were performed and compared at baseline, and 6 months thereafter.

Results: Among the 40 patients initially randomised, 34 patients completed the study (17 patients in the spironolactone group and 17 patients in the placebo group). There was no difference in baseline characteristics or laboratory results between both groups. The spironolactone group showed a significant reduction in CACs at 6 months (169.97 AU [IQR 2.34 - 1146.29] to 92.29 AU [IQR 4.83 - 851.1], p=0.05). Compared to placebo, spironolactone had a lower percentage change in CACs (0% [IQR -47.1-14.7] vs 6.06% [IQR -1.9-40.8], p=0.07. However, the change in the absolute progression of CACs was not different (0 AU [IQR -30.5-58.3] in the spironolactone group vs 6.14 AU [IQR -13.9-331.2] in the placebo group). Spironolactone also showed significantly lower serum phosphorus and osteocalcin (3.8 ± 1.3 mg/dL vs 4.8 ± 1.1 mg/dL and 69.0 ng/mL [IQR 41.9-151.5] vs 178.0 ng/mL [IQR 86.8-269.5], p=0.02 and 0.014, respectively). No hyperkalaemia or hypotension was found in either group.

Conclusion: Among peritoneal dialysis patients, spironolactone showed a potential benefit to prevent the progression of vascular calcification. Further studies with a larger population and long-term follow-up should be conducted.

Keywords: coronary artery calcium score, peritoneal dialysis, vascular calcification, spironolactone

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การศึกษาผลของยาสไปโรโนแลคโตนในการป้องกันการสะสมของผลึกแคลเซียมฟอสเฟต ในผู้ป่วยล้างไตทางช่องท้อง

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาผลของยาสไปโรโนแลคโตนในการป้องกันการสะสมของผลึกแคลเซียมฟอสเฟต และความปลอดภัยในการใช้ยาในผู้ป่วยล้างไตทางช่องท้อง

วิธีดำเนินการวิจัย: การศึกษานี้เป็นการศึกษาแบบสุ่มและมีกลุ่มควบคุมโดยใช้ยาหลอกระหว่างเดือนสิงหาคม พ.ศ. 2561 ถึงเดือนธันวาคม พ.ศ. 2563 ที่โรงพยาบาลวชิรพยาบาล ประเทศไทย สุ่มผู้ป่วยเป็น 2 กลุ่ม กลุ่มได้รับยาสไปโรโนแลคโตน 25 มิลลิกรัมต่อวัน และกลุ่มได้รับยาหลอก เป็นระยะเวลา 6 เดือน โดยทั้ง 2 กลุ่มได้รับการตรวจวัดระดับแคลเซียมในหลอดเลือดหัวใจด้วยเครื่องเอ็กซเรย์คอมพิวเตอร์ (coronary artery calcium scores) และตรวจเลือดทางห้องปฏิบัติการเกี่ยวกับระบบแคลเซียมและหลอดเลือดก่อนเริ่มการวิจัยและหลังเข้ารับการวิจัย

ผลการวิจัย: ผู้ป่วยทั้งหมด 40 คน โดยที่ผู้ป่วย 34 คน จบการศึกษา (ได้รับยาสไปโรโนแลคโตน 17 คน และได้รับยาหลอก 17 คน) โดยรวมทั้งสองกลุ่มมีลักษณะข้อมูลพื้นฐานใกล้เคียงกัน ผลการศึกษาพบว่าการได้รับยาสไปโรโนแลคโตนช่วยลดระดับแคลเซียมในหลอดเลือดหัวใจด้วยเครื่องเอ็กซเรย์คอมพิวเตอร์ได้อย่างมีนัยสำคัญทางสถิติ จาก 169.97 AU (2.34 - 1146.29) เหลือ 92.29 AU ค่า (2.34 - 1146.29) ค่านัยสำคัญทางสถิติ 0.05 นอกจากนี้กลุ่มได้รับยาสไปโรโนแลคโตนยังสามารถลดร้อยละการเปลี่ยนแปลงของระดับแคลเซียมในหลอดเลือดหัวใจด้วยเครื่องเอ็กซเรย์คอมพิวเตอร์ได้มากกว่ากลุ่มยาหลอกร้อยละ 0 (-47.1-14.7) เทียบกับร้อยละ 6.06 (-1.9-40.8) ในกลุ่มยาหลอก (ค่านัยสำคัญทางสถิติ 0.075) ส่วนผลต่างการเปลี่ยนแปลงในกลุ่มยาสไปโรโนแลคโตนได้ 0 AU เทียบกับ 6.14 AU ในกลุ่มยาหลอก (ค่านัยสำคัญทางสถิติ 0.143) ค่าเฉลี่ยการเปลี่ยนแปลงของผลเลือดทางห้องปฏิบัติการพบว่าการได้รับยาสไปโรโนแลคโตนสามารถลดระดับฟอสฟอรัสในเลือดและระดับ osteocalcin ได้อย่างมีนัยสำคัญทางสถิติ โดยที่ผลข้างเคียงไม่พบภาวะโพแทสเซียมในเลือดสูงและความดันโลหิตต่ำทั้ง 2 กลุ่ม

สรุป : การใช้ยาสไปโรโนแลคโตนมีแนวโน้มสามารถป้องกันการสะสมของผลึกแคลเซียมฟอสเฟตได้ในผู้ป่วยล้างไตทางช่องท้องได้ ผู้ศึกษาเสนอแนะให้มีการศึกษาในอนาคตเพื่อดูผลในระยะยาว เพิ่มตัวอย่าง และพิจารณาเพิ่มขนาดยาเพื่อเพิ่มประสิทธิภาพของยา

คำสำคัญ : การตรวจวัดระดับแคลเซียมในหลอดเลือดหัวใจด้วยเครื่องเอ็กซเรย์คอมพิวเตอร์ การล้างไตทางช่องท้อง ภาวะชั้นหินปูนในผนังหลอดเลือด สไปโรโนแลคโตน

วันที่รับบทความ 28 มิถุนายน 2564 **วันแก้ไขบทความ** 15 ธันวาคม 2565 **วันตอบรับบทความ** 15 ธันวาคม 2565

Introduction

Cardiovascular disease is the leading cause of death in patients with chronic kidney disease, including dialysis patients, both haemodialysis and peritoneal dialysis. Several studies have shown a strong relationship between vascular calcification, cardiovascular events and all-cause mortality. Based on clinical practice guideline updates for the diagnosis, evaluation, prevention, and treatment of CKD-MBD[1], it has been suggested that computed tomography-based imaging such as coronary artery calcium score (CACs) can be used to detect the presence or absence of vascular calcification. Many studies have confirmed that high scores for CACs are associated with major adverse cardiac events (MACE), coronary artery disease, and mortality[2-3].

The pathophysiology of vascular calcification is multifactorial and involves an increase in promotors as well as a decrease in the inhibitors of calcifications[4]. Recently, mineralocorticoid receptors were found in vascular smooth muscle cells (VSMC), leading to the hypothesis that hyperaldosteronism may be the cause of vascular calcification. Hyperaldosteronism stimulated mineralocorticoid receptors and triggered osteo-chondrogenic signalling by upregulation of PIT1 expression leading to vascular calcification[5]. Therefore, we hypothesized that spironolactone, which enables mineralocorticoid blockage, can reverse this mechanism and prevent vascular calcification.

The effect of spironolactone for the treatment of vascular calcification was found in klotho-depleted mice[6-7]. Treatment with spironolactone showed a decrease in vascular calcification without a change of calcitriol, FGF-23, serum calcium, and serum phosphate. Matsumoto and colleagues showed that 25 mg/day of spironolactone could reduce morbidity and mortality in haemodialysis patients. However, its use increases the risk of hyperkalaemia, which led to the discontinuation of the study[8]. Moreover, spironolactone showed potential benefits in peritoneal dialysis patients. Yasuhiko and colleagues showed that spironolactone could improve the left ventricular mass index and the left ventricular ejection fraction as well as preserve renal function[9]. A study in Thailand by Yongsiri and colleagues showed spironolactone may be used in the treatment of hypokalemia[10]. None of these studies revealed any serious adverse events.

Since there was no study concerning the administration of spironolactone to prevent vascular calcification in peritoneal dialysis patients, our study was conducted to evaluate this question.

Methods

The study was a prospective randomised double-blinded placebo-controlled trial carried out at Vajira Hospital, Thailand from August 2018 to December 2020. The trial was retrospectively registered at the Thai Clinical Trials Registry (TCTR20221207001) and was approved by the Vajira Institutional Review Board (IRB No. 035/62). The study was conducted in accordance with the Declaration of Helsinki and relevant regulations. The investigators informed patients or their surrogates orally concerning the study, and written informed consent was given before entry into the study.

For inclusion criteria, patients were eligible if they were aged between 18-80 years and had end-stage renal disease receiving peritoneal dialysis. Patients were excluded if they had received spironolactone within the previous 3 months, (2) persistent hyperkalaemia (defined as average serum potassium >5.5 mEq/L within 3 months), (3) persistent hypotension (defined as systolic blood pressure <90 mmHg and diastolic blood pressure <60 mmHg without other antihypertensive drugs), (4) persistent hyperphosphatemia (defined as average serum phosphate >5.5 mg/dL within 3 months), (5) hyperparathyroidism (defined as serum intact PTH >585 pg/mL), (6) dialysis vintage >10 years, (7) life expectancy <1 year due to active malignancy, infection or other diseases, (8) pregnancy or lactation female and (9) post kidney transplant or kidney transplant candidate within the last year.

Hyperkalaemia and hypotension were the most common side effects of spironolactone. Therefore, we defined withdrawal criteria as

persistent hyperkalaemia, defined as serum potassium > 5.5 mEq/L for 2 consecutive times, and hypotension, defined as SBP < 90 mmHg and DBP < 60 mmHg for 2 consecutive times without other antihypertensive drugs. Other adverse events that were or were not considered related to the study drugs were monitored in this study.

Eligible participants were randomised by using a computer-generated block of four to receive either spironolactone 25 mg daily, which was derived from a previous study[8,10], or a placebo for 6 months. Laboratory protocols including serum calcium, phosphorus, intact PTH, alkaline phosphatase, vitamin D levels, and osteocalcin were collected at baseline, 3 months and 6 months. The coronary artery calcium score (CACs) and lateral abdominal radiography were performed at baseline and 6 months thereafter. The CACs were the summation of an area of foci calcification (a calcium threshold of > 130 Hounsfield units) and calculated using the Agatston method. The lateral abdominal X-ray was interpreted using a validated grading system[11-12], of which the extent of calcification was graded on a per-segment basis using the L1-L4 vertebra segments. Per segment, a score between 0 and 3 was given for both the anterior and posterior walls of the aorta. We used scores of at least > 1 to count as vascular calcification. All imaging was read by a single experienced radiologist who was blinded to the study.

All participants were able to receive standard medications such as phosphate binders, vitamin D, erythropoietin and antihypertensive drugs, except spironolactone. However, the participants were asked to avoid over-the-counter drugs and have no adjustment of active vitamin D medication that might interfere with the outcomes.

The primary outcome was the progression of the coronary artery calcium score, consisting of absolute progression, relative progression, and significant progression of CACs. Absolute progression was defined as the difference between the initial and last scores. Relative progression was defined as the ratio between the absolute progression and the initial scores multiplied by 100. The relative progression > 15% was considered a significant progression[13-14].

The secondary outcomes were the effect of spironolactone on the biomarker of mineral-bone disorder, including serum calcium, phosphorus, intact parathyroid hormone (iPTH), alkaline phosphatase (ALP), and osteocalcin, on the effect of spironolactone to vascular calcification in lateral abdominal radiography, on the effect of spironolactone to peritoneal dialysis parameters, and adverse events of spironolactone for long-term use in peritoneal dialysis patients.

Since there was no previous study, we calculated the sample size with α of 0.05 and β of 0.2. The sample size of this study required 30 patients in each group, assumed as a drop-out rate of 10%.

The results were expressed as mean ± standard deviation for continuous normally distributed variables, median, and percentage for categorical variables. Differences in normally distributed variables were evaluated by Student's T-test, non-normal distributed by the Mann-Whitney test, and categorical variables by the Chi-square test. Statistical analysis was performed using SPSS for Windows version 22.0 with $p < 0.05$ considered statistically significant.

Results

From August 2018 to December 2020, a total of 65 patients were assessed for eligibility. A total of 25 patients were excluded, while 40 patients were randomised to receive either the intervention group or the placebo group (figure 1). Three patients in the spironolactone group were withdrawn due to death (2 patients: peritonitis infection and pneumonia with septic shock) and loss of follow-up (1 patient). Three patients in the placebo group were withdrawn due to death (1 patient: intracerebral haemorrhage) and loss of follow-up (2 patients). No follow-up data were available for these patients. In summary, 17 patients in the spironolactone group and 17 patients in the placebo group completed the study.

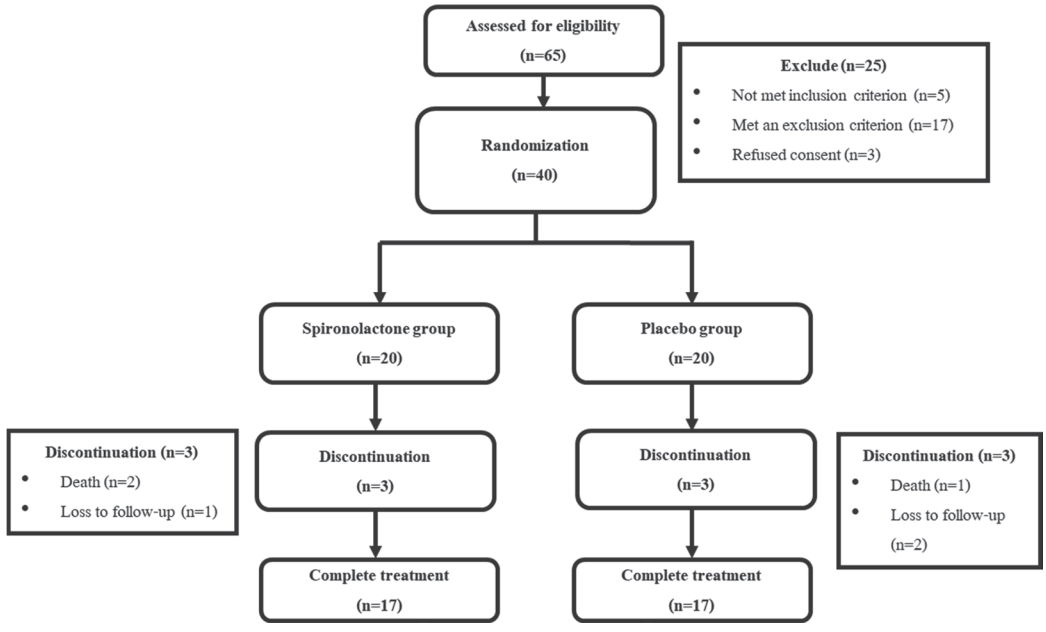

Figure 1 Participants

The baseline characteristics and laboratory data are shown in Table 1. The mean age of patients was 46 ± 15.9 years in the spironolactone group and 54.7 ± 11.9 years in the placebo group, with 64.7% being male. The leading cause of ESRD was diabetic nephropathy. There was a similarity in the medications used for both groups except for the diuretics used, which was higher in the spironolactone group (p=0.037). The baseline laboratory parameters were similar between both groups (table 1). Most of the patients were on continuous ambulatory peritoneal dialysis (CAPD) modality; the dialysis vintage was higher in the placebo group, while residual renal function was higher in the spironolactone group (table 2).

Table 1 Baseline Characteristics

Characteristics	Spironolactone	Placebo
Age, mean ± SD, y	46.0 ± 15.9	54.7 ± 11.9
Sex (Male), n (%)	11 (64.7)	11 (64.7)
Height, mean ± SD, cm	162.5±9.1	163.7 ± 9.5
Body weight, median (IQR), kg	61.0 (53.9-68.5)	59.0 (52.7-77.6)
BMI, median (IQR), kg/m^2	23.4 (20.7-26.4)	22.5 (21.5-28.1)
Underlying disease, n (%)		
Hypertension	15 (88.2)	16 (94.1)
Diabetes mellitus	11 (64.7)	12 (70.6)
Coronary artery disease	6 (35.3)	3 (17.6)

Table 1 Baseline Characteristics (continued)

Characteristics	Spironolactone	Placebo
Cause of ESRD, n (%)		
Diabetic nephropathy	9 (52.9)	10 (58.8)
Hypertensive nephropathy	4 (23.5)	4 (23.5)
SBP, mean ± SD, mmHg	136.2 ± 24.1	147.8 ± 17.0
DBP, mean ± SD, mmHg	79.7±16.2	78.1 ± 10.8
Pulse rate, mean ± SD, bpm	82.9 ± 12.8	77.1 ± 15.6
Medication, n (%)		
ACEi or ARB	6 (35.3)	11 (64.7)
CCB	15 (88.2)	15 (88.2)
Diuretics	13 (76.5)	7 (41.2)
Calcium based phosphate binder	11 (64.7)	12 (70.6)
Non-Calcium based phosphate binder	1 (5.9)	2 (11.8)
Active vitamin D	1 (5.9)	6 (35.3)
Laboratory		
Hb, mean ± SD, g/dL	10.7 ± 1.7	10.2 ± 1.1
BUN, mean ± SD, mg/dL	53.4 ± 17.3	50.5 ± 22.9
Creatinine, mean ± SD, mg/dL	9.17± 4.80	9.38±3.92
Potassium, mean ± SD, mEq/L	3.7 ± 0.6	3.9 ± 0.6
Bicarbonate, mean ± SD, mEq/L	29.7 ± 2.6	28.8 ± 3.1
Calcium, mean ± SD, mg/dL	8.3 ± 0.9	8.1 ± 1.0
Phosphate, mean ± SD, mg/dL	4.3 ± 1.0	3.9 ± 0.8
Albumin, mean ± SD, mg/dL	2.9 ± 0.5	2.7 ± 0.6
iPTH, mean ± SD, pg/dL	274.9 ± 142.5	295.9 ± 125.1
Vitamin D level, mean ± SD, ng/mL	14.8 ± 10.9	17.0 ± 11.4
Osteocalcin, mean ± SD, ng/mL	148.4 ± 123.2	225.8 ± 155.8
ALP, mean ± SD, U/L	68.7 ± 33.9	117.7 ± 60.11

Data are presented as n (%), mean ± SD, or median (interquartile range).
Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ALP, alkaline phosphatase; ARB, angiotensin receptor blocker; BMI, Body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; Hb, haemoglobin; iPTH, intact parathyroid hormone; SBP, systolic blood pressure

Table 2 Baseline Peritoneal dialysis data

Peritoneal dialysis data	Spironolactone	Placebo	p-value
Mode of peritoneal dialysis, n (%)			0.60
CAPD	16 (94.1)	14 (82.4)	
APD	1 (5.9)	3 (17.6)	
Dialysis vintage, n (%), y			0.11
<1	10 (58.8)	6 (35.3)	
1-5	7 (41.2)	7 (41.2)	
>5	0 (0.0)	4 (23.5)	
Net ultrafiltration volume (mL)	600 (350-900)	800 (275-800)	0.85
Residual renal function, n (%), mL			0.035
<100	2 (11.8)	9 (52.9)	
100-500	7 (41.2)	2 (11.8)	
>500	8 (47.1)	6 (35.3)	
Peritoneal equilibrium test, n (%)			0.47
High	4 (23.5)	7 (41.2)	
High-average	9 (52.9)	6 (35.3)	
Low-average	4 (23.5)	4 (23.5)	
Dialysis adequacy (≥ 1.7) , n (%)	12 (70.6)	14 (82.4)	0.69

Data are presented as n (%) or median (interquartile range).
p-value: comparison baseline value between spironolactone group and control group; Mann-Whitney U test, Chi-square test and Fisher's exact test

The median coronary artery calcium scores (CACs) in the spironolactone group decreased statistically from 169.97 AU (IQR 2.34 – 1146.29) to 92.29 AU (IQR 4.83 – 851.1), p=0.05. In contrast, the CACs in the placebo group decreased from 424.96 AU (IQR 59.68 - 1346.34) to 450.73 AU (IQR 64.44 - 1716.17), p=0.96. The median absolute progression was lower in the spironolactone group compared to the control group, 0.00 AU (IQR -30.47 - 58.29) vs 6.14 AU (IQR -13.89 - 331.23), p=0.14. The median relative progression of CACs was also lower in the spironolactone group, 0% (IQR -47.15 - 14.69) vs 6.06% (IQR -1.87 - 40.83), p=0.07. Significant CACs progression in patients (progression of CACs more than 15%) was higher in the placebo group, but there was no statistical significance. The subgroup analysis based on the severity of CACs demonstrated no significant difference in either subgroup (table 3).

The spironolactone group had a significant decrease in mean serum iPTH (from 274.9 ± 142.5 pg/ml to 227.9 ± 123.1 pg/ml, p-value 0.045). The placebo group showed a significant increase in mean serum phosphate (from 3.9 ± 0.8 mg/dL to 4.83 ± 1.1 mg/dL, p-value 0.019). The changes in other biochemical markers of mineral-bone disorder such as mean serum calcium, mean serum vitamin D, mean serum osteocalcin and mean serum alkaline phosphatase revealed no significant differences within the group. However, there were significant differences in mean serum phosphate and mean serum osteocalcin between the spironolactone group and the placebo group (p-values of 0.02 and 0.014, consecutively) (table 4).

Table 3 Progression of coronary artery calcium scores

	Spironolactone	Placebo	p-value[b]
Coronary artery calcium scores (CACs)			
Baseline, median (IQR), AU	169.97 (2.34 - 1146.29)	424.96 (59.68 - 1346.34)	0.51
Final, median (IQR), AU	92.29 (4.83 - 851.1)	450.73 (64.44 - 1716.17)	0.22
p-value[a]	0.05	0.96	
Absolute progression, median (IQR), AU	0.00 (-30.47 - 58.29)	6.14 (-13.89 - 331.23)	0.14
Relative progression, median (IQR), %	0 (-47.15 - 14.69)	6.06 (-1.87 - 40.83)	0.07
Progression > 15 %, n (%)	4 (23.5)	7 (41.2)	0.27
Subgroup analysis			
CACS 0-100 (n=12)			
Relative progression, median (IQR), %	0 (-58.87 - 23.29)	0 (0 - 100)	0.32
Progression > 15 %, n (%)	2 (25.0)	1 (25.0)	1.00
CACS 101-399 (n=6)			
Relative progression, median (IQR), %	-23.92 (-45.7 - -2.14)	-2.28 (-11.83 - 28.49)	0.36
Progression > 15 %, n (%)	0 (0.0)	1 (25.0)	1.00
CACS ≥400 (n=16)			
Relative progression, median (IQR), %	8.74 (-48.61 - 17.15)	27.41 (1.16 - 40.83)	0.13
Progression > 15 %, n (%)	2 (28.6)	5 (55.6)	0.36

Data are presented as median (interquartile range) and n (%).
p-value[a] : comparison within group by Wilcoxon signed-rank test, p-value[b] : comparison between spironolactone group and control group by Mann-Whitney U test
CACs, coronary artery calcium score

As shown in Table 4, the spironolactone group was significantly decreased in terms of vascular calcification compared to the placebo group (p-value 0.031).

There was no difference in residual renal function or net ultrafiltration volume between both groups. The number of patients who had a reduction in residual renal function showed no significant difference between groups, with no patients in the spironolactone group and one patient in the placebo group (p-value 0.27). There was no significant difference in the mean net ultrafiltration volume between groups (800 ml in the spironolactone group and 800 ml in the placebo group, p-value 0.48).

No hyperkalaemia or hypotension was found in this study. The spironolactone group had 2 patients who died from infected peritonitis and pneumonia with septic shock. Meanwhile, the placebo group had a patient who died from intracerebral haemorrhage. The other adverse events are reported in Table 5.

Table 4 Change in biochemical parameters

	Spironolactone		Placebo		p-value[b]
	Baseline	Final	Baseline	Final	
Hb, g/dL	10.7 ± 1.7	10.1 ± 2.1	10.2 ± 1.1	10.5 ± 1.2	0.40
BUN, mg/dL	53.4 ± 17.3	47.8 ± 18.1	50.5 ± 22.9	52.1 ± 22.8	0.55
Creatinine, mg/dL	9.2 ± 4.8	9.3 ± 5.2	9.4 ± 3.9	9.9 ± 4.0	0.72
Potassium, mEq/L	3.7 ± 0.6	3.7 ± 0.4	3.9 ± 0.6	3.7 ± 0.6	0.89
Bicarbonate, mEq/L	29.7 ± 2.6	30.0 ± 2.3	28.8 ± 3.1	28.3 ± 2.6	0.05
Calcium, mg/dL	8.3 ± 0.9	7.9 ± 0.7	8.1 ± 1.0	7.9 ± 0.9	0.95
Phosphate, mg/dL	4.3 ± 1.0	3.8 ± 1.3	3.9 ± 0.8	4.8 ± 1.1[a]	0.02
Albumin, mg/dL	2.9 ± 0.5	2.8 ± 0.6	2.7 ± 0.6	2.7 ± 0.4	0.79
iPTH, pg/dL	274.9 ± 142.5	227.9 ± 123.0[a]	295.9 ± 125.1	299.0 ± 228.4	0.27
Vitamin D level, ng/mL	12.1 (6.9-18.2)	17.7 (11.0-29.9)	11.8 (8.9-25.5)	20.6 (13.2-25.6)	0.62
Osteocalcin, ng/mL	119.0 (47.1-195.5)	69.0 (41.9-151.5)	216.0 (94.5-282.0)	178.0 (86.8-269.5)	0.014
ALP, U/L	68.7 ± 33.9	86.1 ± 38.5	117.7 ± 60.1	106.0 ± 59.8	0.26
Lateral abdominal radiography					0.031
No calcification	11 (64.7)	14 (82.4)	7 (41.2)	8 (47.1)	
Calcification	6 (35.3)	3 (17.6)	10 (58.8)	9 (52.9)	

Data are presented as n (%), mean ± SD, or median (interquartile range).
p-value[a] comparison within group by Paired sample t-test, Wilcoxon signed-rank test, and McNemar's test.
p-value[b] comparison final value between spironolactone group and control group; Mann-Whitney U test, and Chi-square test.
Abbreviations: Hb, haemoglobin; BUN, blood urea nitrogen; iPTH, intact parathyroid hormone

Table 5 Adverse events

	Spironolactone	Placebo
Minor adverse event	4 (20%)	3(15%)
Nausea and vomiting	0	2(10%)
Gynecomastia	2(10%)	0
Common cold	2(10%)	1(5%)
Hyperkalaemia	0(0%)	0(0%)
Hypotension	0(0%)	0(0%)
Serious adverse event		
Infected peritonitis	3(15%)	1(5%)
Volume overload	2(10%)	2(10%)
Pneumonia	1(5%)	0
Sepsis	0	1(5%)
Seizure	1(5%)	0
Intracerebral haemorrhage	0	1(5%)
Death	2(10%)	1(5%)

Data were presented as n (%)

Discussion

SV-CAPD was the first pilot randomised double-blind placebo-controlled trial to demonstrate the efficacy of spironolactone to prevent the progression of vascular calcification in peritoneal dialysis patients. Despite the impressive results of spironolactone in klotho-depleted mice, our study showed 25 mg of spironolactone daily had no statistical significance in decreasing the progression of CACs compared to placebo. The absolute progression and relative progression of CACs were lower in the spironolactone group, but there was no statistical significance.

The administration of spironolactone to prevent vascular calcification using CACs was first demonstrated by Gueiros and colleagues in Brazil[15]. The result was comparable to our study in that spironolactone tended to prevent the progression of CACs. However, that study had some limitations such as small sample size and limitations of the blind. Our study utilised a larger sample size with 40 patients enrolled, and 34 patients who completed the study. Interestingly, our study showed a significant decrease in CACs in the spironolactone group (169.97 AU [IQR 2.34 - 1146.29] to 92.29 AU [4.83 - 851.1], p=0.05) compared to the placebo group, which was no improvement in CACs (424.96 AU [IQR 59.68 - 1346.34] to 450.73 AU {[IQR 4.44 - 1716.17], p=0.96). When comparing the relative progression of CACs, however, which was the more accurate result for interpretations of the progression of CACs, the efficacy of spironolactone was better but showed no statistical significance (0 AU [IQR -47.15 - 14.69] vs 6.06 AU [IQR -1.87 - 40.83], p=0.07. The result was the same with the absolute progression of CACs (table 3).

The mechanism of spironolactone to prevent vascular calcification was the inhibition of the mineralocorticoid receptors on vascular smooth muscle cells (VSMC). In our study, spironolactone had a significant improvement in serum osteocalcin levels. Since serum osteocalcin was a marker of bone formation, spironolactone may prevent the progression of vascular calcification as a result of this mechanism[16-17]. However, one of the potential causes of improvement in CACs in the spironolactone group may be from the enhanced control of serum phosphate. In our study, the mean serum phosphate at the end of the study was decreased in the spironolactone group compared to the placebo group. In contrast to previous studies[18], spironolactone did not affect serum phosphate. Thus, the spironolactone group might have better dietary phosphate control than the placebo group, or there was an unknown mechanism of spironolactone to decrease serum phosphate.

In this pilot study, we did not demonstrate the other potential benefits of spironolactone in peritoneal dialysis, such as cardiovascular outcomes, improvement of hypokalaemia, or prevention of the progression of peritoneal fibrosis. However, our study showed the safety of spironolactone for long-term use. In contrast to haemodialysis patients[8], the adverse effects of spironolactone, such as hyperkalaemia and hypotension, were not found in our study. Other adverse events were not significantly different in either group (2 deaths in the spironolactone group and 1 death in the placebo group). Therefore, our study assured that spironolactone 25 mg per day should be noted to be safe for long-term use in peritoneal dialysis patients.

Our study had several strengths. Firstly, our study was the first randomised double-blinded placebo-controlled trial to demonstrate the effect of spironolactone in preventing the progression of vascular calcification. Secondly, spironolactone is cost-effective, so it can be widely used in both well-resourced and limited-resourced facilities to prevent vascular calcification in peritoneal dialysis patients. Moreover, our study also showed the safety of spironolactone for long-term use in peritoneal dialysis patients.

Our study also had several limitations. Firstly, it used a low number of patients. We calculated a sample size of 60 patients, but only 40 patients undertook the study. Secondly, short follow-up periods were used. Previous trials had suggested a

follow-up period for the CACs of 12 to 24 months. However, some studies[20] showed the benefit of spironolactone to decrease left ventricular hypertrophy during a 6-month follow-up period. As a pilot study, we showed the effect of spironolactone to potentially prevent vascular calcification with 6-month follow-up periods. A longer follow-up period could show significant effects. Thirdly, the CACs in the spironolactone group were lower than in other previous cohort studies[19]. In our study, the CACs in the spironolactone group were 169.97 AU (IQR 2.34 - 1146.29), while the previous cohort study was 492 AU (IQR 92-1139). Finally, the dosage of spironolactone was fixed at 25 mg/day. Therefore, increasing the dose might improve the outcomes.

Conclusion

Spironolactone tends to prevent the progression of the coronary artery calcium score. A large population and a longer follow-up period are needed to confirm this hypothesis. Since there was no hyperkalaemia or hypotension in our study, the dose of spironolactone could be increased to attenuate the effects.

Conflicts of Interest

All authors declare that they have no conflicts of interest.

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Clinical Manifestations of Pulmonary Tuberculosis in Childhood

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Abstract

Objective: To determine clinical presentations related to pulmonary tuberculosis in children.

Methods: A retrospective descriptive study was conducted in children less than 15 years old who were diagnosed with pulmonary tuberculosis at the Department of Pediatrics, Faculty of Medicine Vajira Hospital between January 1st, 2009 - January 1st, 2021. The quantitative data were analyzed into mean and standard deviation and compared between groups by unpaired t-test. The qualitative data were reported by percentage and compares between groups by Chi-square test.

Results: A total of 96 patients were included. The average age was 10.3 ± 4.6 years (6 months to 15 years old); 36.5% of patients were male and 63.5% were female, while 84.4% of the patients presented with 2 or more clinical features. Signs and symptoms described in the Thai CPG for Tuberculosis in Children 2019 that were found in this study were cough ≥ 2 weeks (58.3%), fever ≥ 7 days (57.3%), anorexia (42.7%), weight loss (25.0%), inactivity (8.3%), and poor weight gain (1%). Signs and symptoms not included in the Thai CPG for Tuberculosis in Children 2019 were afebrile (34.4%), cough < 2 weeks (28.1%), fatigue (28.1%), hemoptysis (19.8%), night sweat (15.6%), no cough (13.5%), dyspnea (12.5%), chest pain (9.4%), tachypnea (9.4%), fever < 7 days (8.3%), lymphadenopathy (8.3%), chronic vomiting and diarrhea (1%), and asymptomatic (2.1%). Ninety-two patients (95.8%) always had at least 1 clinical feature that was described in the Thai Tuberculosis CPG 2019. However, 4 patients (4.2%) in this study only presented with clinical features not included in the Thai Tuberculosis CPG 2019, including 1 patient who presented with only chest pain, 1 patient who presented with only hemoptysis, and 2 asymptomatic patients.

Conclusion: Most of the pediatric patients with pulmonary tuberculosis presented with 2 or more clinical features and almost always had at least 1 symptom that was described in the Thai Tuberculosis CPG 2019.

Keywords: childhood, pulmonary tuberculosis, clinical manifestations

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ลักษณะทางคลินิกของวัณโรคปอดในเด็ก

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาอาการและอาการแสดงที่เป็นไปได้ของผู้ป่วยเด็กที่ได้รับการวินิจฉัยวัณโรคปอด

วิธีดำเนินการวิจัย: ทำการศึกษาเชิงพรรณนาย้อนหลัง ในผู้ป่วยอายุน้อยกว่า 15 ปี ที่ได้รับการวินิจฉัยวัณโรคปอดในภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์วชิรพยาบาล ระหว่างวันที่ 1 มกราคม พ.ศ. 2552 ถึงวันที่ 1 มกราคม พ.ศ. 2564 วิเคราะห์ข้อมูลเชิงปริมาณด้วยค่าเฉลี่ย และส่วนเบี่ยงเบนมาตรฐาน เปรียบเทียบค่าเฉลี่ยระหว่างกลุ่มโดย unpaired t-test วิเคราะห์ข้อมูลเชิงคุณภาพด้วยการนำเสนอเป็นร้อยละ เปรียบเทียบระหว่างกลุ่มโดย Chi-square test

ผลการวิจัย: พบผู้ป่วยเด็กจำนวน 96 ราย อายุเฉลี่ย 10.3 ± 4.6 ปี (6 เดือน - 15 ปี) เป็นผู้ป่วยชายร้อยละ 36.5 ผู้ป่วยหญิงร้อยละ 63.5 ที่ได้รับการวินิจฉัยวัณโรคปอด พบว่าผู้ป่วยร้อยละ 84.4 มีอาการ ≥ 2 อาการขึ้นไปร่วมกัน โดยพบอาการที่อยู่ในแนวทางเวชปฏิบัติการรักษาวัณโรคในเด็ก พ.ศ. 2562 ได้แก่ ไอมากกว่าหรือเท่ากับ 2 สัปดาห์ (ร้อยละ 58.3) ไข้มากกว่าหรือเท่ากับ 7 วัน (ร้อยละ 57.3) เบื่ออาหาร (ร้อยละ 42.7) น้ำหนักลดไม่ทราบสาเหตุ (ร้อยละ 25.0) ซึม ไม่เล่น (ร้อยละ 8.3) และน้ำหนักไม่เพิ่มขึ้น (ร้อยละ 1) พบอาการที่นอกเหนือจากแนวทางเวชปฏิบัติการรักษาวัณโรคในเด็ก พ.ศ. 2562 ได้แก่ ไม่มีไข้ (ร้อยละ 34.4) ไอน้อยกว่า 2 สัปดาห์ (ร้อยละ 28.1) อ่อนเพลีย (ร้อยละ 28.1) ไอเป็นเลือด (ร้อยละ 19.8) เหงื่อออกกลางคืน (ร้อยละ 15.6) ไม่ไอ (ร้อยละ 13.5) หายใจลำบาก (ร้อยละ 12.5) เจ็บหน้าอก (ร้อยละ 9.4) หายใจเร็ว (ร้อยละ 9.4) ไข้น้อยกว่า 7 วัน (ร้อยละ 8.3) คลำได้ก้อนต่อมน้ำเหลือง (ร้อยละ 8.3) อาเจียนและถ่ายเหลวเรื้อรัง (ร้อยละ 1) และไม่มีอาการ (ร้อยละ 2.1) ผู้ป่วย 92 คน (ร้อยละ 95.8) เป็นผู้ที่มีอาการและอาการแสดงที่อยู่ในแนวทางเวชปฏิบัติการรักษาวัณโรคในเด็ก พ.ศ. 2562 ร่วมด้วยอย่างน้อย 1 อาการ อย่างไรก็ตาม พบผู้ป่วย 4 ราย (ร้อยละ 4.2) ในการศึกษานี้ที่มีเฉพาะอาการที่ไม่อยู่ในแนวทางเวชปฏิบัติการรักษาวัณโรคในเด็ก พ.ศ. 2562 ได้แก่ เจ็บหน้าอกอย่างเดียว 1 ราย ไอเป็นเลือดอย่างเดียว 1 ราย และไม่มีอาการ 2 ราย

สรุป: ผู้ป่วยเด็กที่เป็นวัณโรคปอด ส่วนมากมีอาการและอาการแสดงตั้งแต่ 2 อาการขึ้นไป และเกือบทั้งหมดมีอาการและอาการแสดงที่อยู่ในแนวทางเวชปฏิบัติการรักษาวัณโรคในเด็ก พ.ศ. 2562 ร่วมด้วยอย่างน้อย 1 อาการ

คำสำคัญ: เด็ก วัณโรคปอด ลักษณะทางคลินิก

วันที่รับบทความ 18 เมษายน 2565 **วันแก้ไขบทความ** 16 ธันวาคม 2565 **วันตอบรับบทความ** 16 ธันวาคม 2565

Introduction

Thailand is one of the 22 high-burden tuberculosis countries on the WHO's list[1]. The estimated number of incidences is around 120,000 cases per year[2], but the incident reports for childhood tuberculosis in Thailand are markedly lower than in other countries[1]. Identifying and treating TB infections in children provides long-term benefits in TB control. However, diagnosis of TB in children is a difficult task because of its unspecific signs and symptoms[3] and radiological findings[4]. Moreover, microbiological confirmations are hard to obtain because younger patients are unlikely to expectorate sputum as effectively as adults[5].

The Thai Clinical Practice Guideline of Treatment for Tuberculosis in Children 2019[2] was established to help diagnose tuberculosis in children based on clinical features (fever more than 7 days, cough more than 2 weeks, weight loss, poor weight gain, inactivity, and anorexia) along with contact exposures and/or tuberculin skin test and radiographic findings.

Previous studies showed that weight loss[6-7], chronic cough[7-8], and fatigue[7-8] were significantly associated with pulmonary tuberculosis in children whereas persistent fever and/or chest pain were found in 25% of the patients[8]. However, some of patients diagnosed with pulmonary tuberculosis presented with fever of less than 7 days[9-10] and cough less than 14 days[10]. Devrim I found that 13% of children diagnosed with pulmonary tuberculosis presented without fever, cough, malaise, and weight loss at the same time[11]. In addition, 2-44.6% of patients were reported to have other symptoms such as dyspnea[9,12], night sweat[11], hemoptysis[12-13], diarrhea[9], vomiting[9], hepatomegaly[9], and lymphadenopathy[9], or were asymptomatic[9].

The diagnosis of pulmonary tuberculosis in children is a major challenge due to various clinical features. This study aimed to determine the typical signs and symptoms of pulmonary tuberculosis according to the Thai CPG of Treatment for Tuberculosis in Children 2019, as well as signs and symptoms that are not included in the CPG. This information may provide benefits for clinicians to recognize typical and atypical signs and symptoms of pulmonary tuberculosis, which may improve screening and treatment for pulmonary TB.

Methods

This is a retrospective descriptive study. The study protocol was reviewed and approved by the Ethics Committee for Research in Humans, Institutional Review Board (COA 059/2563). The inclusion criteria were patients younger than 15 years old at the Department of Pediatrics, Faculty of Medicine Vajira Hospital, Navamindradhiraj University who were diagnosed with pulmonary tuberculosis from January 1st, 2009 - January 1st, 2021. The exclusion criteria were patients with latent tuberculosis infection, congenital tuberculosis, extrapulmonary tuberculosis, immunocompromised host or receiving immunosuppressive agents, and incomplete medical record.

Criteria for the diagnosis of pulmonary tuberculosis were defined according to the Thai Clinical Practice Guideline of the Treatment of Tuberculosis in Children 2019 that considers 3 elements of the following for diagnosis: 1) Signs and symptoms compatible with tuberculosis: fever > 7 days (persistent unexplained fever > 38°C reported by a guardian or objectively recorded at least once[14]), weight loss (an unexplained reduction of weight of more than 5% within 3 months[14]), poor weight gain (inability to maintain the percentile curve of the growth chart or a percentile drop during the period prior to TB diagnosis[9]), inactive (unexplained lethargy or decrease in activity reported by a parent or caregiver[14]), cough > 2 weeks (persistent, non-remitting cough > 2 weeks[14]) and anorexia; 2) Contact with a TB index case or a positive result for tuberculin skin test (TST), and 3) Abnormal radiographic finding such as hilar adenopathy, Ghon's complex, intrapulmonary calcification, miliary infiltration, cavity, lobar or segmental atelectasis, or pleural effusion. Pulmonary tuberculosis was defined as one of the following:

1) Patients who presented with all three criteria; 2) Patients who presented with signs and symptoms and abnormal radiographic findings who did not improve after receiving treatment for bacterial pneumonia, and 3) Patients with military infiltration.

Statistical analysis

A sample size of 96 was estimated by the infinite population size formula[15]

$$n = \frac{Z_{\alpha/2}{}^2\, p(1-p)}{d^2}$$

in which p is the prevalence of signs and symptoms in a pediatric patient with pulmonary tuberculosis in line with the research of Tarunotai U.[12], (p = 0.514), acceptable type I error is set at 5% ($\alpha = 0.05$) and d (Error) equal to 0.1

The statistical analysis was performed using SPSS version 22.0. The quantitative data such as age and weight were analyzed into means and standard deviations and compared between groups by unpaired t-test. The qualitative data such as the result of microbiological confirmations, criteria for diagnosis, and clinical manifestations were reported by percentage and compared between groups by Chi-square test.

Results

This study collected data from pediatric patients at Vajira Hospital who were diagnosed with pulmonary tuberculosis from January 1st, 2009 - January 1st, 2021. A total of 96 patients were included (figure 1). Thirty-five patients (36.5%) were male and 61 (63.5%) patients were female, with an age ranging from 6 months to 15 years old. The average age was 10.3 ± 4.6 years and most of the children were 10 to 15 years old. Among the cases, 8.3% had underlying diseases, including 2 patients with asthma and one patient each with bronchiectasis, G6PD deficiency, congenital cystic adenomatoid malformation, epilepsy, Down syndrome, and thalassemia (table 1).

There were 78.2% of the patients who met all three criteria of Thai Clinical Practice Guideline of the Treatment of Tuberculosis in Children 2019 as shown in Table 1, with 36.5% of this group having at least one microbiological confirmation. There were 18.8% of the patients who met only two criteria, including clinical features and radiological abnormality, but because of their positive microbiological results, the diagnosis can be made.

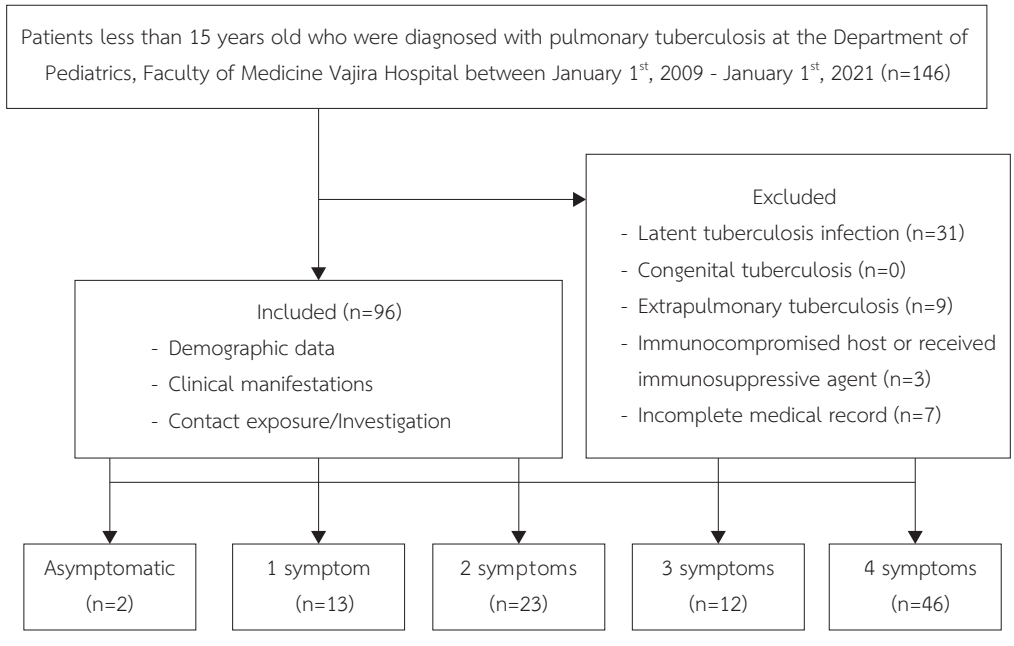

Figure 1 Subjects flowchart

Table 1:
Demographic data of childhood pulmonary TB patients (n=96)

	Number (%)
Age distribution (years)	
<1 year	3 (3.1)
1-4 years	13 (13.5)
5-9 years	17 (17.7)
10-15 years	63 (65.6)
Body weight (percentile)	
< P3	4 (4.2)
P3 – P97	83 (86.4)
≥ P97	9 (9.4)
TB contact history	59 (61.5)
TST positive	54 (81)
Microbiological examination	
AFB positive	47 (51.6)
Culture for M. tuberculosis positive	14 (16.9)
PCR for M. tuberculosis positive	7 (30)
Criteria diagnosis for pulmonary TB	
Clinical + TST/Contact history + Radiological finding	40 (41.7)
Clinical + TST/Contact history + Radiological finding + Microbiological confirmation	35 (36.5)
Clinical + Radiological finding + Microbiological confirmation	18 (18.8)
TST/Contact history + Radiological finding	2 (2.1)
Clinical + Radiological finding	1 (1.0)

There were 2 cases (2.1%) who were asymptomatic, and met only the two criteria of contact history and abnormal CXR findings; both were treated with anti-TB drugs. The chest x-ray findings improved as the treatment was completed. There was 1 patient, a 13-year-old boy, who presented with hemoptysis of 1 week, who had been diagnosed with pulmonary TB only from clinical and radiological criteria, with neither a history of TB contact nor positive TST, and the microbiological confirmation was also negative. The CXR showed reticular infiltration in both upper lungs, therefore, CT chest was performed as an additional investigation. The findings were infiltration and consolidation at the right upper lung and left upper lung, with a tree-in-bud pattern, suggesting pulmonary TB. The patient was treated with anti-TB drugs and was successfully cured.

The outcome of the treatment revealed that 86 (89.6%) of the children were cured, 6 (6.3%) continued treatment at other hospitals, 4 (4.2%) were lost to follow up and none died.

The most common of the signs and symptoms in our study was cough (86.5%), followed by fever (65.6%), anorexia (42.7%), fatigue (28.1%), weight loss (25%), and hemoptysis (19.8%) as displayed in Table 2. There were 4 patients (4.2%) without any signs and symptoms described in the Thai Clinical Practice Guideline of the Treatment of Tuberculosis in Children 2019[2], including one patient who presented with only chest pain, another with only hemoptysis, and 2 patients without any symptoms.

Table 2 Clinical manifestations of childhood pulmonary TB patients

Signs and symptoms described in Thai Clinical Practice Guideline of Treatment for Tuberculosis in Children 2019*	Number (%)
Cough ≥ 2 weeks	56 (58.3)
Fever ≥ 7 days	55 (57.3)
Anorexia	41 (42.7)
Weight loss	24 (25.0)
Inactive	8 (8.3)
Poor weight gain	1 (1.0)
Signs and symptoms not included in Thai Clinical Practice Guideline of Treatment for Tuberculosis in Children 2019*	**Number (%)**
Afebrile	33 (34.4)
Cough < 2 weeks	27 (28.1)
Fatigue	27 (28.1)
Hemoptysis	19 (19.8)
Night sweat	15 (15.6)
No cough	13 (13.5)
Dyspnea	12 (12.5)
Tachypnea	9 (9.4)
Chest pain	9 (9.4)
Fever < 7 days	8 (8.3)
Lymphadenopathy	8 (8.3)
Chronic vomiting and diarrhea	1(1.0)
Asymptomatic	2 (2.1)

*Each patient may have more than 1 of the signs and/or symptoms.

In 63 patients presenting with fever, 55 of them (87.3%) had a fever for more than 7 days; 8 (12.7%) had fever for fewer than 7 days, while 33 (34.4%) patients were afebrile. Therefore 41 of 96 patients (42.7%) had a fever for fewer than 7 days or had no fever. Also, in 83 patients presenting with cough, 56 (64.7%) had a cough for more than 2 weeks and 27 (32.5%) had a cough for less than 2 weeks, while 13 (13.5%) patients did not have a cough. Hence, 40 of 96 patients (41.6%) had a cough for less than 2 weeks or did not have a cough at all.

Thirty patients (31.2%) were reported to have both fever for more than 7 days and cough for more than 2 weeks, whereas 15 (15.6%) had both fever for fewer than 7 days and cough for less than 2 weeks. The number of patients with either fever for more than 7 days or cough for more than 2 weeks was 81 (84.4%).

Most of the patients (47.9%) presented with 4 or more clinical features, 13 (13.5%) presented with 1 symptom, 23 (24%) presented with 2 symptoms, 12 (12.5%) presented with 3 symptoms, and 2 (2.1%) were asymptomatic, as shown in Table 3. The maximum number of symptoms (8 symptoms) was found in 1 patient, including fever, cough, hemoptysis, tachypnea, dyspnea, chest pain, fatigue, and night sweat.

Table 3 Summary of signs and symptoms for each individual patient

	Number (%)
1 symptom	13 (13.5)
Only cough ≥ 2 weeks	8 (8.3)
Only fever ≥ 7 days	3 (3.1)
Only hemoptysis*	1 (1.0)
Only chest pain*	1 (1.0)
2 symptoms	23 (24.0)
Fever ≥ 7 days and cough ≥ 2 weeks	6 (6.3)
Cough ≥ 2 weeks and hemoptysis*	5 (5.2)
Fever ≥ 7 days and cough < 2 weeks*	4 (4.2)
Cough ≥ 2 weeks and anorexia	4 (4.2)
Cough < 2 weeks* and anorexia	2 (2.1)
Cough ≥ 2 weeks and chest pain*	1 (1.0)
Fever ≥ 7 days and fatigue*	1 (1.0)
3 symptoms	12 (12.5)
Cough ≥ 2 weeks, hemoptysis* and fatigue*	2 (2.1)
Fever ≥ 7 days, cough ≥ 2 weeks and weight loss	2 (2.1)
Fever ≥ 7 days, weight loss and lymphadenopathy*	2 (2.1)
Fever ≥ 7 days, cough ≥ 2 weeks and anorexia	2 (2.1)
Fever ≥ 7 days, cough < 2 weeks* and anorexia	1 (1.0)
Fever < 7 days*, cough < 2 weeks* and anorexia	1 (1.0)
Fever ≥ 7 days, cough < 2 weeks* and hemoptysis*	1 (1.0)
Fever ≥ 7 days, cough < 2 weeks* and fatigue*	1 (1.0)
≥ 4 symptoms	46 (47.9)
No symptoms	2 (2.1)

* Not included in the Thai Clinical Practice Guideline of Treatment for Tuberculosis in Children 2019

Discussion

A majority of the patients (78.2%) met all three diagnostic criteria for pulmonary tuberculosis described in the Thai Clinical Practice Guideline of Treatment for Tuberculosis in Children 2019[2] with or without having the microbiological confirmation for diagnosis. Among this group, 2.1% of the patients only had symptoms that were not included in the Thai Tuberculosis CPG 2019[2] (only chest pain and only hemoptysis at the time of presentation), while 18.8% of the patients met only two criteria, including clinical features and radiological abnormality, but because of their positive microbiological results, the diagnosis can be made. There were 2.1% of the patients who were asymptomatic and were diagnosed with pulmonary tuberculosis due to a history of

contact tuberculosis and abnormal radiological findings, while 1% of the patients had clinical features and abnormal radiological findings without a history of contact with tuberculosis. Therefore, the Thai CPG of Treatment for Tuberculosis in Children 2019[2] can establish the diagnosis of pulmonary TB in most of the patients, but there are some limitations in those who have a history of contact exposure but are asymptomatic or presented with symptoms not included in the CPG.

In our study, signs and symptoms described in the Thai CPG 2019[2] were reported, including cough for more than 2 weeks (58.3%), fever for more than 7 days (57.3%), anorexia (42.7%), weight loss (25%), inactivity (8.3%), and poor weight gain (1%). Cough and fever are the main symptoms of pulmonary tuberculosis, as reported by Devrim I[11] and Tarunotai U[12] who stated that cough and fever were reported in 81.5 – 94.4% and 33.7 – 71.4%, respectively. Anorexia was also found in a study from Marais BJ[6] (22.2%). The number of patients who had weight loss in this study was close to that of the study of Marais BJ[6] (27.8%). Nevertheless, most of the patients did not have all of the signs and symptoms that were included in the Thai tuberculosis CPG[2] at the same time. We found that 84.4% presented with 2 or more clinical features, and among those were clinical features both included and not included in this CPG.

Signs and symptoms not included in the Thai tuberculosis CPG 2019[2] that were found in this study included afebrile (34.4%), cough for less than 2 weeks (28.1%), no cough (13.5%), and fever for less than 7 days (8.3%). There were 15.6% of patients who presented with neither cough for more than 2 weeks nor fever for more than 7 days, which was relatively lower than in Zar HJ[10] (21%) and Soriano-Arandes A[9] (38.6%). Other signs and symptoms not mentioned in the Thai tuberculosis CPG 2019[2] that were also found in this study were as follows: fatigue (28.1%), hemoptysis (19.8%), night sweat (15.6%), dyspnea (12.5%), tachypnea (9.4%), and chest pain (9.4%). These were clinical features that were also reported in Marais BJ[6]. In addition, 8.3% of the patients in this study had lymphadenopathy, which was slightly higher than in Soriano-Arandes A[9] and Limpokaiyakul P[13] in which lymphadenopathy was found in 2% and 4.4% of the patients, respectively. Chronic diarrhea and vomiting were reported in 1% of the patients, which was also reported in Soriano-Arandes A[9] who found 5% of the patients presented with vomiting and 6.9% presented with diarrhea. In addition, there were asymptomatic patients reported at 2.1% in this study, which was lower than in Devrim I[11] and Marais BJ[6] (13-50%).

Most of the patients who presented with clinical features not included in Thai tuberculosis CPG 2019[2] almost always had other clinical features that were described in this CPG concurrently, making the diagnosis of pulmonary tuberculosis more convenient. However, 4 patients (4.2%) in this study were an exception. They presented with only clinical features not included in tuberculosis CPG 2019[2] including 1 patient who presented with only chest pain, 1 patient with only hemoptysis, and 2 asymptomatic patients. Therefore, other information, such as history of contact exposure or radiographic features compatible with pulmonary tuberculosis became an important factor for making the diagnosis of pulmonary tuberculosis in childhood.

The limitation of this study is that we gathered information in a retrospective manner, using data collected from medical records in the past, so some of the data may be incomplete or have information errors due to recording errors.

Conclusion

The clinical features of pulmonary tuberculosis in childhood are varied. Patients may have signs and symptoms included or not included in the Thai Clinical Practice Guideline of Treatment for Tuberculosis in

Children 2019. A majority of the patients had 2 or more symptoms, while 95.8% of the patients had at least 1 symptom described in the CPG and could be diagnosed with pulmonary TB based on clinical symptoms described in the Thai CPG criteria. Only 4.2% presented with clinical features not included in the CPG and were diagnosed based on contact exposure or radiographic features compatible with pulmonary tuberculosis. This made the Thai CPG a suitable guideline for the diagnosis of pulmonary tuberculosis in childhood.

Conflict of interest

The authors declare no conflict of interest.

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- Age-Related Neck Circumference in Habitually Snoring Children: A Potential Screening Tool for Obstructive Sleep Apnea in Children
  (เส้นรอบวงคอตามเกณฑ์อายุในเด็กที่นอนกรนประจำมีศักยภาพเป็นเครื่องมือคัดกรองภาวะหยุดหายใจขณะหลับจากการอุดกั้นในเด็กหรือไม่)
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- Results of Posteromedial Capsule and Superficial Medial Collateral Ligament Release on Gap and Alignment in Total Knee Arthroplasty for Varus Knee Deformity by Computer-Assisted Surgery Measurement
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- Clinical Manifestations of Pulmonary Tuberculosis in Childhood
  (ลักษณะทางคลินิกของวัณโรคปอดในเด็ก)

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