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MINIREVIEWS

Is mandible derived mesenchymal stromal cells superior in proliferation and regeneration to long bone-derived mesenchymal stromal cells?

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Abstract

Mesenchymal stromal cells (MSCs) are cells with the characteristic ability of self-renewal along with the ability to exhibit multilineage differentiation. Bone marrow (BM) is the first tissue in which MSCs were identified and BM-MSCs are most commonly used among various MSCs in clinical settings. MSCs can stimulate and promote osseous regeneration. Due to the difference in the development of long bones and craniofacial bones, the mandibular-derived MSCs (M-MSCs) have distinct differentiation characteristics as compared to that of long bones. Both mandibular and long bone-derived MSCs are positive for MSC-associated markers such as CD-73, -105, and -106, stage-specific embryonic antigen 4 and Octamer-4, and negative for hematopoietic markers such as CD-14,

-34, and -45. As the M-MSCs are derived from neural crest cells, they have embryogenic cells which promote bone repair and high osteogenic potential. *In vitro* and *in vivo* animal-based studies demonstrate a higher rate of proliferation and high osteogenic potential for M-MSCs as compared to long-bones MSCs, but *in vivo* studies in human subjects are lacking. The BM-MSCs have their advantages and limitations. M-MSCs may be utilized as an alternative source of MSCs which can be utilized for tissue engineering and promoting the regeneration of bone. M-MSCs may have potential advantages in the repair of craniofacial or orofacial defects. Considering the utility of M-MSCs in the field of orthopaedics, we have discussed various unresolved questions, which need to be explored for their better utility in clinical practice.

Key Words: Mandible; Long bone; Mesenchymal stromal cells; Osteogenic potential; Regeneration

Core Tip: Due to the difference in the development of long bones and craniofacial bones, the mandibular-derived MSCs (M-MSCs) have distinct differentiation characteristics as compared to that of long bones. In vitro and *in vivo* animal-based studies demonstrate a higher rate of proliferation and high osteogenic potential for M-MSCs as compared to long-bones MSCs, but *in vivo* studies in human subjects are lacking. Considering the utility of M-MSCs in the field of orthopaedics, we have discussed various unresolved questions, which need to be explored for their better utility in clinical practice.

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INTRODUCTION

Mesenchymal stromal cells (MSCs) are cells with the ability to self-renew along with the ability to exhibit multilineage differentiation[1,2]. Initially, they were identified from the murine bone marrow (BM) as "plastic-adherent cells", which are mainly generated from the fibroblast colony-forming units (CFU-F). Friedenstein *et al*[3] first identified CFU-F by isolating adherent cells from the BM stroma of newborn rodents which can form discrete colonies. However, these cells are regulated by various mitogenic factors such as epidermal growth factor, platelet-derived growth factor, transforming growth factor-β, basic fibroblast growth factor, and insulin growth factor-1[4-6].

Previously, MSCs were given much attention due to their precious role in creating a supportive microenvironment in the hematopoietic tissue but later their precursor role was identified for the formation of skeletal tissue/bone[7,8]. MSCs in adults have been studied extensively in animals as well as humans and have been isolated from various tissues such as BM of long bones (including ilium, femur, tibia) and mandibular bone[9-11].

International Society for Cellular Therapy has suggested the identification criteria for mesenchymal progenitors i.e. these cells can express CD-73, -90, and -105 but cannot express CD-11b or -14, -19 or -79a, -34, -45, -34 and human leukocyte antigen (HLA) -DR[12,13]. MSCs are used in the treatment of non-healing ulcers or wounds, for promoting bone regeneration in cases with non-healing or delayed healing, and MSCs can differentiate into various tissue-specific cell types, which can promote angiogenesis. Treatment with these cells has shown promising results in wound healing by various mechanisms such as promoting re-epithelialization, improving granulation tissue, promoting angiogenesis, and reducing inflammatory reactions. MSCs are utilized in the management of chronic non-healing ulcers, diabetic ulcers, bed/pressure sores, and radiation-induced burns[14].

An electronic search was conducted until Dec 2022 including articles from January 2003 to December 2022 databases such as PubMed, Web of Science, Embase, and CNKI (China Knowledge Resource Integrated Database). The terms used for the search included: "mesenchymal stromal cell", "MSCs", "mandible", "long bone", "regenerative potential", "proliferation", and "regeneration". In this manuscript, we compared the proliferation and regenerative potential of mandible and long bones.

BONE MARROW-DERIVED MSCS

Bone marrow is the first tissue in which MSCs were identified and BM-MSCs are most commonly used in clinical settings. The Food and Drug Administration registered the first drug derived from BM-MSCs called "prochymal", a drug against Graft *vs* Host Disease[15]. MSCs derived from the BM have a unique ability to proliferate and differentiate into various cell types in the culture i.e. fibroblasts, chondrocytes, osteocytes, adipocytes, myogenic cells, *etc*. Apart from this, MSCs also can secrete potent bioactive cytokines, which help the MSCs to regulate other cell types[16-18]. MSCs can be obtained from BM of long bones which are appendicular bones derived from the mesoderm. However, maxillary and mandibular bones develop from the neural crest cells[19]. These differences in the development of the long bone and mandibular bones may reflect the difference in the properties of progenitor cells derived from different BM sites. Previous studies have reported phenotypic and functional differences in laboratory studies for cell proliferation, adipogenic potential, osteogenic potential, efficiency to form colonies, and cell surface markers[20-22]. These cells have therapeutic significance i.e. they can stimulate bone growth and promote the regeneration of the bone. MSCs have been suggested to be beneficial in the management of fractures with delayed union or non-union. These cells are documented to have certain advantages; first, these cells can migrate to the site of injury and promote regeneration; secondly, these cells suppress the local immune response; third, the quantity of the MSCs can be obtained in large amounts from patients themselves[23].

Overall, the efficacy of MSCs has been established *in vitro* studies. However, the survival of these cells *in vivo* largely depends upon depends on cell survival, osteogenic differentiation, and host cell recruitment. The major limiting factor affecting the therapeutic potential of MSCs is their low survival rates following transplantation. Literature suggests that transplanted MSCs cannot survive in the presence of temporal hypoxia or a harsh microenvironment where the MSCs of the donor are not able to survive and eventually undergo apoptosis[24]. The advantages of BM-MSCs include high stability in the culture, feasible accessibility to harvesting sites, and high osteogenic potential. The disadvantages of BM-MSCs include the painful BM harvesting process and the risk of infection by the procedure[25].

MANDIBLE DERIVED MSCS

The maxillofacial region is one of the richest sources of BM-MSCs. This region is comprised of bones particularly jaw bones, dental tissues, blood vessels, nerves, adipose tissue, and muscular tissue[11]. The MSCs from BM of the mandible (jaw) was first described in 2005 by Matsubara *et al*[20]. Neural crest cells [cranial, vagal, trunk, and cardiac] help in the development of the peripheral nervous system, orofacial and cranial bones including the mandible, melanocytes, smooth muscle cells, and endocrine cells[26,27]. The intramembranous ossification leads to the formation of craniofacial bones.

Features of M-MSCs

Due to the difference in the development of long bones and craniofacial bones, M-MSCs have distinct differentiation characteristics as compared to long bones[20,21]. Yamaza *et al*[28] studied the features of M-MSCs isolated from the mouse. They reported that M-MSCs are capable of forming adherent colonies due to the presence of a colony-forming unit (CFU) and the number of colonies was $55.3 \pm 9.07/1.5 \times 10^6$ cells/plate. The potential of doubling and rate of cell proliferation of M-MSCs are much higher than BM-MSCs. M-MSCs are positive for MSC-associated markers such as CD-73, -105, and -106, stage-specific embryonic antigen 4 (SSEA-4), and Octamer-4 (Oct-4) whereas it is negative for hematopoietic markers such as CD-14, -34, and -45. M-MSCs are weakly positive for c-Kit and strongly positive for Sca-1 (stem cell antigen-1).

In vitro evidence of superiority in lineages of M-MSCs

Lee *et al*[29] investigated the role of M-MSCs *in vitro* studies and observed the formation of mineral nodules as early as 14 d of the osteogenic differentiation, which tends to increase over time till 21 d. These cells can suppress T lymphocytes and thus have been recommended in acute graft *vs* host disease. Li *et al*[24] observed the growth of M-MSCs within 2 to 3 d of the culture and the proliferation time was also documented to be much earlier *in vitro* study. Cytometric analysis revealed strong expression of CD-29, -73, -90, and -105. M-MSCs have higher osteogenic and mineralization potential as compared to femoral BM-MSCs, but the serial passage *in vitro* reduces differentiation potentials[29]. Yamaza *et al*[28] observed M-MSCs from mice to have stronger suppressive effects on anti-CD3 antibody proliferation which activates T cells thereby suppressing T cell activation. M-MSCs produce NO in a higher amount as compared to BM-MSCs when stimulated with IFN-γ. The multilineage differentiation under osteogenic conditions revealed their differentiation into osteoblasts with increased activity of serum alkaline phosphatase (ALP) and increased mineralized nodule formation. Also, these cells exhibit higher expression of osteoblastic markers such as osteocalcin, RunX2, and ALP.

In vivo evidence of superiority in lineages of M-MSCs

Lee *et al*[29] reported a significantly higher rate of mineralization in the rat calvarial defects implanted with gel foam with M-MSCs as compared with gel foam only. The volume of new bone was 80.88% ± 0.68% for the gel foam with the M-MSCs group and only 49.87% ± 0.94% for only the gel foam group. Overall, M-MSCs have reported higher osteogenic potential with high site-specific bone regeneration capacity[20,21]. Various studies have documented the osteogenic potential of M-MSCs which helps in bone regeneration[30-32]. Deluiz *et al*[33] in their rat model study demonstrated that M-MSCs inoculation significantly promoted bone formation at 4 wk (22.75 ± 2.25 mm^3) as well as at 8 wk (64.95 ± 5.41 mm^3) as compared to acellular bone microparticles (2.34 ± 2.91 mm^3 and 42.73 ± 10.58 mm^3 at 4 wk and 8 wk respectively). The TRAP and osteocalcin-positive cells were also higher on immunohistochemical analysis at 4 wk in the cell-seeded group as compared to the acellular group. Yamaza *et al*[28] transplanted M-MSCs into immunocompromised mice along with a carrier [hydroxyapatite/tricalcium phosphate (HA/TCP)] and demonstrated increased osteogenic potential in the form of increased bone formation.

LONG BONE-DERIVED MSCS

MSCs were initially derived from the long appendicular bones and these bones are the principal source of MSCs in clinical settings owing to their feasible accessibility. The appendicular bones develop from mesoderm[34]. The most common location among the appendicular bone for isolation of MSCs is the iliac crest. The alternative sites include long bones (tibia, femur, humerus, radius) and sternum[34]. Literature suggests that MSCs properties as well as graft retaining properties of MSCs may vary depending upon harvesting sites[35].

Features of long bone-derived MSCs

As the sites of BM aspiration of appendicular bones are easily accessible, aspiration is easy[35]. These cells are positive for MSC-associated markers such as CD-29, -44, -73, -90, -105, -166, and HLA-ABC and negative for hematopoietic markers such as CD-14, -34, and -45[28,35]. The osteogenic potential of the MSCs helps in bone regeneration and bone repair. The MSCs have been utilized in the management of delayed union or non-union of fracture, osteogenesis imperfecta, osteoporosis, *etc.* Also, the MSCs can differentiate into chondrocytes, adipocytes, osteocytes, *etc*[36].

In vitro evidence in lineages of long bone-derived MSCs

Li *et al*[37] observed the appearance of colonies of femur-derived MSCs (F-MSCs) was scantly on the 2nd or 3rd day. Cytometric analysis revealed strong expression of CD-29, -73, -90, and -105. The cells derived from F-MSCs have osteogenic and mineralization potential, and the serial passage *in vitro* does not reduce the ability of differentiation of these cells. Proliferation is delayed but the cloning rate is higher. The osteogenic potential as evidenced by ALP lasted beyond 21 d. Lee *et al*[29] investigated the role of F-MSCs *in vitro* study and observed mineralization within 14 days these cells express CD-44, -72, -90, and -105, but failed to express CD-34 and -45.

In vivo evidence in lineages of long bone-derived MSCs

The F-MSCs have increased osteogenic potential when transplanted into immunocompromised mice as evidenced by the increased bone formation in a study by Yamaza *et al*[28]. Aghaloo *et al*[22] observed a primarily cartilaginous matrix following long bone-derived MSC implantation with good osteoblastic differentiation. The periosteum of long bones contains mesenchymal progenitors which have high proportions of EdU (DNA synthesis probe)-positive cells and possess the highest clonogenic ability. Apart from this, these progenitors have a lower rate of apoptosis with high proliferative properties[38]. A comparison of mandible *vs* long bone-derived MSCs is depicted in Table 1.

COMPARISON OF MSCS FROM FEMUR, TIBIA, HUMERUS, RADIUS, AND ILIUM

Recently, MSCs have been harvested from BM of long bones such as the femur (proximal and distal), tibia, humeral head, radius, ilium, *etc*[39,40]. The posterior part of the iliac crest is preferred for obtaining autologous stem cells as it contains the highest amount of nucleated cells (25.1–54.7) × 10^6 cells/mL, whereas the concentration of nucleated cells in the anterior iliac crest is (24.4–49) × 10^6 cells/mL. However, the mean number of nucleated cells in decreasing concentration has been reported from the proximal humerus (38.7 × 10^6 cells/mL), followed by the distal femur (25.9 × 10^6 cells/mL), humeral head, and proximal tibia (12.1 × 10^6 cells/mL)[39]. Mc Daniel *et al*[41] observed the highest BM aspirate, higher nucleated cells, and highest CFUs from the iliac crest. However, CFUs from bone marrow aspirate (BMA) of the iliac crest, femur, tibia, and humerus were 12692.3 ± 4981.4, 11235.2 ± 3451.6, 9433.9 ± 4065.1, and 9347.3 ± 3366.3 respectively whereas that from concentrated BMA aspirates, highest

Table 1 Comparison of mandible *vs* long bone-derived MSCs

Ref.	Features	Mandible derived MSCs	Long bone-derived MSCs
Lee *et al*[35], 2011	Aspiration time	10 min	2 min
Yamaza *et al* [28], 2011	No. of colonies	55.3 ± 9.07/ 1.5 × 10^6 cells/plate (Higher)	5.33 ± 0.58/ 1.5 × 10^6 cells/plate
Li *et al*[37], 2019		The appearance of colonies was early within 2-3 d of inoculation into the culture	The appearance of colonies of Femur- MSCs was scantly on the 2nd or 3rd day as compared to M-MSCs
Yamaza *et al* [28], 2011	Osteogenic potential	High	Low
Matsubara *et al*[20], 2005		High	Low
Aghaloo *et al* [22], 2010		higher activity of ALP and OCN expression suggesting higher osteogenic potential	Comparatively lower osteogenic potential
Li *et al*[37], 2019		After 21 d, M-MSCs showed loss of morphology, and dry staining was observed; *Runx2* gene expression was higher	After 21 d, F-MSCs showed obvious cell morphology
Yamaza *et al* [28], 2011	Doubling rate and cell proliferation	High	Low
Lee *et al*[29], 2019		Proliferation time (OD-0.82 ± 0.26) was also documented to be much earlier as compared to F-MSCs but doubling time was lower (22.6 ± 2.22 h)	Proliferation time was much delayed (OD-1.13 ± 0.41) as compared to M-MSCs but doubling time was earlier (35 ± 3.19 h)
Li *et al*[37], 2019		Proliferation time was also documented to be much earlier as compared to F-MSCs	Proliferation time was much delayed as compared to M-MSCs
Li *et al*[37], 2019	Arrangement of cells	On day 2, triangular, while after cell (tightly) fusion- these cells are arranged as paving stones	On day 2, elongated fibroblast-like morphology, while after cell (tightly) fusion- F-MSCs show vortex-like cloning center
Yamaza *et al* [28], 2011	Cell expression	Positive for MSC-associated markers such as CD-73, -105, and -106, SSEA-4, and Oct-4; Negative for hematopoietic markers such as CD-14, -34, and -45; Expresses SSEA-4 (6.4%) and Oct-4 (6%) in much higher proportion as compared to long bones	Positive for MSC-associated markers such as CD-73, -105, and -106, SSEA-4, and Oct-4; Negative for hematopoietic markers such as CD-14, -34, and -45. Expresses SSEA-4 (4.2%) and Oct-4 (2.6%) in lower proportion
Lee *et al*[35], 2011		Negative for hematopoietic stem cells such as for CD-14, -34, -45, and HLA-DR whereas positive for MSC markers such as CD-29, -44, -73, -90, -105, -166, and HLA-ABC	Negative for hematopoietic stem cells such as for CD-14, -34, -45, and HLA-DR whereas positive for MSC markers such as CD-29, -44, -73, -90, -105, -166, and HLA-ABC
Li *et al*[37], 2019		Strongly expressed CD-29, -73, -90, and -105 but negative for CD-31 and -34	Strongly expressed CD-29, -73, -90, and -105 but negative for CD-31 and -34
Aghaloo *et al* [22], 2010	Mineralization	Mandible BMSC were significantly larger and calcification was also more as compared to long bones; Tissue volume and bone volume was also larger	Less calcified as compared to M-MSCs
Lee *et al*[29], 2019		Mineralization appears within 14 d of osteogenic differentiation (mean-1.57 ± 0.05)	The mineral formation is higher (1.98 ± 0.05) as compared to M-MSCs at 14 d
Aghaloo *et al* [22], 2010	Histology	Characterized by increased and mature lamellar bone with marked osteoblastic rimming of bony trabeculae	The bone formed was primarily of the cartilaginous matrix with only peripheral bone formation

ALP: Alkaline phosphatase; BMSC: Bone mesenchymal stem cell; HLA: Human leukocyte antigen; MSCs: Mesenchymal stromal cells; M-MSCs: Mandibular-derived MSCs; F-MSCs: Femur-derived MSCs; OCN: Osteocalcin; SSEA-4: Stage-specific embryonic antigen 4; Oct-4: Octamer-4.

CFU was obtained from the iliac crest, followed by tibia, femur and least was from humerus.

LACUNAE IN UNDERSTANDING M-MSCS

Though M-MSCs has been utilized in animal studies and their osteogenic potential, immunomodulatory effect and clinical utility have been documented, studies in human are lacking and the mechanism depicting *in vivo* potential in therapeutic and clinical setting needs further elucidation. The factors affecting these cells when transplanted *in vivo* such as route of inoculation, time, indication for inoculation, and location of their inoculation need to be explored. Autologous M-MSCs potential is explored in previous studies, and literature elucidating the roles of allogenic M-MSCs in bone repair/ regeneration with risks of rejection needs further exploration. Despite the utility of M-MSCs in the field

of orthopaedics, there remain various unresolved questions, which need to be explored for their better utility in clinical practice.

AUTHOR'S OPINIONS

BM-MSCs have adherent properties that form the colonies and have osteogenic potential with the characteristic ability to differentiate into various types of cells such as osteoblasts, chondrocytes, adipocytes, *etc*. Irrespective of sites, BM-MSCs can suppress T lymphocytes and cell-mediated immunity supporting its utility in graft *vs* host disease. Concerning the accessibility and ease of obtaining the BM-MSCs, long bones are superior and the cells could be obtained as early as 2 min. However, the risk of infection is high[25] in the case where BM is derived from long bones. M-MSCs have a significantly higher number of CFUs, high proliferation rate, higher ALP activity, and high osteogenic potential as compared to MSCs derived from long bones, especially during the initial 14 d[28,41]. For the prolonged duration, the MSCs derived from BM-MSCs had higher activity and less apoptosis. The doubling time and cloning time are also superior for MSC derived from long bones as compared to M-MSCs. Therefore, we recommend the regenerative medicine researchers and experts to explore the regenerative potential of mandible derived MSCs in chondrogenesis and osteogenesis.

CONCLUSION

MSCs are of therapeutic significance for bone repair and regeneration. As M-MSCs are derived from neural crest cells, they have embryogenic cells which promote bone repair and have high osteogenic potential. *In vitro* and *in vivo* animal-based studies demonstrate a higher rate of proliferation and higher osteogenic potential for M-MSCs as compared to long-bones-derived MSCs, but *in vivo* studies including human subjects are still lacking. BM-MSCs have their advantages and limitations. M-MSCs may be utilized as an alternative source of MSCs which can be utilized for tissue engineering and promoting the regeneration of bone. M-MSCs may have potential advantages in the repair of craniofacial or orofacial defects.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Urinary tract injury during hysterectomy: Does surgeon specialty and surgical volume matter?

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Abstract

BACKGROUND

Ureteral injury is a known complication of hysterectomies. Recent studies have attempted to correlate surgeon volume and experience with incidence of urinary tract injuries during hysterectomies. Some studies have reported that as surgeon volume increases, urinary tract injury rates decrease. To our knowledge, no studies have assessed the relationship between surgeon subspecialty and the rate of urinary tract injury rates during minimally invasive hysterectomy.

AIM

To determine the incidence of urinary tract injury between urogynecologists, gynecologic oncologists, and general gynecologists.

METHODS

The study took place from January 1, 2016 to December 1, 2021 at a large community hospital in Detroit, Michigan. We conducted a retrospective chart review of adult patients who underwent minimally invasive hysterectomy. After we identified eligible patients, the surgeon subspecialty was identified and the surgeon's volume per year was calculated. Patient demographics, medical history, physician-dictated operative reports, and all hospital visits postoperatively were reviewed.

RESULTS

Urologic injury occurred in four patients (2%) in the general gynecologist group, in one patient (1%) in the gynecologic oncologist group, and in one patient (1%) in

the urogynecologist group. When comparing high and low-volume surgeons, there was no statistically significant difference in urinary tract injury (1% *vs* 2%) or bowel injury (1% *vs* 0%). There were more complications in the low-volume group *vs* the high-volume group excluding urinary tract, bowel, or major vessel injury. High-volume surgeons had four (1%) patients with a complication and low-volume surgeons had 12 (4%) patients with a complication (P = 0.04).

CONCLUSION
Our study demonstrated that there was no difference in the urinary tract injury rate in general gynecologists *vs* subspecialists, however our study was underpowered.

Key Words: Minimally invasive hysterectomy; Urinary tract injury; Surgeon volume; High volume gynecologist; Low volume gynecologist

Core Tip: Surgeon volume and experience have been shown to play a role in decreasing the number of urinary tract injuries during minimally invasive hysterectomies. One may conclude that since urogynecologists and gynecologic oncologists had additional training years after residency, they also have more experience. This may result in a decreased incidence of urinary tract injury during minimally invasive hysterectomies. To our knowledge, no studies to date have been done to assess this correlation.

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INTRODUCTION

Hysterectomy is a common gynecologic surgery in the United States. It is estimated that there are over three hundred thousand hysterectomies performed each year[1]. Ureteral injury is a known complication of hysterectomies, and it is estimated that between 52 and 82 percent of all iatrogenic urinary tract injuries occur during gynecology surgeries[2]. Studies have reported iatrogenic ureteral injury incidence as low as 0.18%[3] and as high as 2.2%[4]. These injuries increase the rates of patient morbidity and mortality such as sepsis and fistula formation[5].

The method of hysterectomy has been examined to assess this risk of urinary tract injury. Janssen *et al*[4] found that those undergoing abdominal hysterectomy had an increased risk of ureteral injury when compared with vaginal hysterectomy. Another study found that the incidence of urinary tract injury was lowest in laparoscopic supracervical hysterectomy (LSH), compared to laparoscopic assisted vaginal hysterectomy (LAVH) and total laparoscopic hysterectomy (TLH)[6].

More recently, surgeon volume and experience have been studied when assessing risk factors for urinary tract injury during hysterectomies. Vree *et al*[7] reported that high-volume surgeons (those performing greater than 51 hysterectomies per year) had shorter operative time and less estimated blood loss, but no difference in the rate of urinary tract injury when compared with low-volume surgeons (those performing less than 11 hysterectomies per year). However, another study demonstrated that patients who underwent benign hysterectomy by a high-volume surgeon (greater than 14.1 hysterectomies per year), were less likely to have bladder, ureteral, and intestinal injury when compared with those surgeons who performed less than 5.88 hysterectomies per year[8]. Janssen *et al*[4] reported that as surgeon experience increased, defined by a threshold of greater than 30 hysterectomies performed, the risk of ureter injury decreased from 2.2% to 0.5%. To our knowledge no studies have been performed evaluating the effect of surgeon subspecialty on urinary tract injury rates during minimally invasive hysterectomy.

MATERIALS AND METHODS

We conducted a retrospective chart review of adult patients who underwent minimally invasive hysterectomy (including laparoscopic and robotic methods) with and without concomitant procedures from January 1, 2016 to December 1, 2021. All procedures and postoperative care were done at a large urban hospital by a fellowship trained board-certified female pelvic medicine and reproductive surgery

(FPMRS) surgeon (also known as a urogynecologist), fellowship trained board eligible or board-certified gynecologic oncology surgeons, and board-certified general gynecologists. All patients who underwent the following surgeries with or without concomitant procedures were included: LSH, LAVH, TLH, and robotic hysterectomy. After we identified eligible patients, the surgeon subspecialty was identified and the surgeon's volume per year was calculated. Patient demographics, medical history, physician-dictated operative reports, and all hospital visits postoperatively were reviewed. Our primary outcome was the incidence of urinary tract injury between fellowship trained board-certified FPMRS surgeon, fellowship trained board eligible or board-certified gynecologic oncology surgeons, and board-certified or board eligible general gynecologists. Our secondary outcome was the incidence of urinary tract injury between high (defined by 30 or more minimally invasive hysterectomies per year) and low-volume surgeons (defined by less than 30 hysterectomies per year). To calculate a power analysis for our study, we used data reported by Mäkinen *et al*[9], who cited the rate of urinary tract injury as 4.4% and 1.3% for low- (less than 30 hysterectomies per year) and high-volume (equal to or greater than 30 hysterectomies per year) surgeons respectively. To show such an effect, with 80% power and alpha = 0.05, at least 452 patients were needed in each group, for a total of 904 patients. Descriptive statistics were generated to characterize the subjects. Continuous variables were described as the mean with standard deviation or median with 25th and 75th percentiles. Categorical variables were described as frequency distributions. Univariable analysis of factors associated with surgeon type and ureteral injury were assessed using Student's t-test, analysis of variance (ANOVA) followed by multiple pairwise comparisons using the Bonferroni correction of the *P* value, and the χ^2 analysis. Non-parametric tests were performed for data that were non-normally distributed, such as the Mann-Whitney U test and Kruskal-Wallis test. Analyses were conducted with SPSS version 25.0 and a *P* value less than 0.05 was considered to indicate statistical significance. All statistical analysis of this study were performed and/or reviewed by biomedical statisticians Karen Hagglund, MS and Susanna Szpunar, MPH, DrPH.

RESULTS

Primary outcome

In total 523 patients underwent minimally invasive hysterectomies performed during the study period. General gynecologists performed 255, the urogynecologist performed 196, and the gynecologic oncologists performed 102 procedures. Patient demographics are reported in Table 1. Patients in the general gynecologist group were younger than those in the urogynecologist and gynecologic oncologist groups. Patient race differed between groups. Patient history of cardiovascular disease differed between groups with those in the general gynecologist group having lesser incidence of cardiovascular disease ($P < 0.0001$). The average body mass index (BMI) also varied between groups with those in the urogynecologist (29.2 ± 6.3) having a lower BMI than those in the general gynecologist (32.6 ± 7.7) and gynecologic oncology (34.4 ± 9.2) groups ($P < 0.0001$).

Operating time and estimated blood loss also differed between groups. Across all time parameters (total set-up time, total operating time, and total room time), the urogynecologist had the longest times, followed by the gynecologic oncologist and then the general gynecologists ($P < 0.0001$). The urogynecologist [25.0 (20, 50)] had the least blood loss, while the general gynecologists [100 (50, 200)] had the most ($P < 0.0001$). These results can be found in Table 2. Length of stay did not differ between groups ($P = 0.93$) and can also be found in Table 2. Surgery type and concomitant procedures are detailed in Table 3. The urogynecologist performed more concomitant cystourethroscopies (100%) when compared to the general gynecologists (41%) and gynecologic oncologists (29%, $P < 0.0001$). The urogynecologist also performed more ureterolysis procedures (6%) than the general gynecologists (1%) and gynecologic oncologists (2%, $P = 0.01$). The general gynecologists performed less lysis of adhesions (22%) in comparison to the urogynecologist (35%) and gynecologic oncologist (34%, $P = 0.004$). Two percent of patients in both the general gynecologist and gynecologic oncologist groups underwent conversion to an open procedure. No procedures in the urogynecologist group underwent conversion to an open procedure.

Urologic injury occurred in four patients (2%) in the general gynecologist group, in one patient (1%) in the gynecologic oncologist group, and in one patient (1%) in the urogynecologist group. Bowel injury occurred in three (3%) of patients in the gynecologic oncologist group and there were none in the general gynecologist and urogynecologist groups. There were no cases of major vessel injury.

Secondary outcomes

A total of 42 surgeons performed minimally invasive hysterectomies at our institution during the specified time frame and were included in our study. Three of these surgeons performed 30 or more minimally invasive hysterectomies per year and qualified to be placed in the high-volume surgeon category. There were 280 patients in the high-volume group and 273 patients in the low-volume group. Patient demographics can be found in Table 4. Patient age and race differed between groups. Patient history of cardiovascular disease, hypertension, diabetes mellitus, and BMI also differed between groups. Total set up time, total operating time, and total room time all were significantly longer for

Table 1 Patient demographics-subspecialty, *n* (%)

	General gynecologist, *n* = 255; mean ± SD	Urogynecologist, *n* = 196; mean ± SD	Gynecologic oncologist, *n* = 102; mean ± SD	*P* value
Age (yr)	45.4 ± 8.3	58.9 ± 12.5	55.9 ± 11.3	< 0.0001
Race				0.001
Black	94 (37)	42 (21)	19 (18)	
White	146 (57)	139 (71)	73 (72)	
Other/Unknown	15 (6)	15 (8)	10 (10)	
BMI	32.6 ± 7.7	29.2 ± 6.3	34.4 ± 9.2	< 0.0001[a]
Cardiovascular disease	41 (16)	70 (36)	27 (27)	< 0.0001
Hypertension	83 (33)	86 (44)	48 (47)	0.01
Diabetes mellitus	25 (10)	24 (12)	18 (18)	0.12
Chronic lung disease	44 (17)	27 (14)	16 (16)	0.62
History of abdominal surgery	160 (63)	109 (56)	55 (54)	0.18

[a]Urogynecologist *vs* general gynecologist and gynecologic oncologist, $P < 0.0001$, general gynecologist *vs* gynecological oncologist, $P = 0.12$. BMI: Body mass index.

Table 2 Surgery characteristics and length of stay-subspecialty

	General gynecologist, *n* = 255; mean ± SD or median (25th %ile, 75th %ile)	Urogynecologist, *n* = 196; mean ± SD or median (25th %ile, 75th %ile)	Gynecologic oncologist, *n* = 102; mean ± SD median (25th %ile, 75th %ile)	*P* value
Total set-up time (minutes)	34.3 ± 8.2	51.1 ± 7.7	40.7 ± 9.8	< 0.0001[a]
Total operating time (minutes)	133.1 ± 57.8	257.8 ± 48.9	162.4 ± 69.2	< 0.0001[a]
Total room time (minutes)	192.1 ± 61.5	343.0 ± 51.9	231.1 ± 74.5	< 0.0001[a]
Uterine weight (grams)	181.2 ± 131.1	104.1 ± 72.7	150.9 ± 104.3	< 0.0001[b]
Estimated blood loss (mL)	100.0 (50, 200)	25.0 (20, 50)	50.0 (50, 100)	< 0.0001
Length of stay (d)	1.0 ± 0.7	1.1 ± 0.2	1.0 ± 0.5	0.93

[a]All comparisons, $P < 0.0001$.
[b]General gynecologist *vs* urogynecologist, $P < 0.0001$; general gynecologist *vs* gynecological oncologist, $P = 0.06$; urogynecologist *vs* gynecological oncologist, $P = 0.002$.

high-volume surgeons compared to low-volume surgeons. These comparisons can be found in Table 5. Uterine weight was higher in the low-volume surgeon group (179.0 0 ± 129.6) when compared to the high-volume surgeon group (117.50 ± 85.4, $P < 0.0001$). Low-volume surgeons also had an increased estimated blood loss when compared to high-volume surgeons [100.0 mL (50, 200) and 50.0 mL (20, 50) respectively, $P < 0.0001$]. The length of stay did not differ between groups. Patients in the high-volume group stayed 1.0 d ± 0.4 and those in the low-volume surgeon group stayed on average 1.0 d 0 ± 0.7 ($P = 0.98$).

High-volume surgeons performed mostly robotic hysterectomies (86%), while low-volume surgeons performed mostly LAVH (53%). While high-volume surgeons did perform ureterolysis more often than low-volume surgeons (5% *vs* 1%, $P = 0.01$), there was no significant difference in lysis of adhesions (31% *vs* 26%, $P = 0.17$). High-volume surgeons performed cystourethroscopy more often than low-volume surgeons (74% *vs* 44%, $P < 0.0001$). Two (1%) patients in the high-volume group were converted to open,

Table 3 Surgery type and concomitant procedures-subspecialty, *n* (%)

	General gynecologist, *n* = 255	Urogynecologist, *n* = 196	Gynecologic oncologist, *n* = 102	*P* value
Surgery				--
LAVH	144 (57)	0 (0)	25 (24)	
LSH	13 (5)	0 (0)	1 (1)	
TLH	47 (18)	0 (0)	13 (13)	
RATLH	50 (20)	196 (100)	63 (62)	
Concomitant procedures				--
None	19 (8)	0 (0)	1 (1)	
BS	168 (66)	13 (7)	13 (13)	
BSO	66 (26)	2 (10	88 (86)	
BS+SC	0 (0)	34 (17)	0 (0)	
BSO+SC	0 (0)	116 (59)	0 (0)	
SC	0 (0)	3 (2)	0 (0)	
BS+USLS	1 (0)	18 (9)	0 (0)	
BSO+USLS	1 (0)	7 (3)	0 (0)	
USLS	0 (0)	3 (2)	0 (0)	
Rectopexy	2 (1)	31 (16)	0 (0)	--
Cystourethroscopy	105 (41)	194 (99)	30 (29)	< 0.0001
Lysis of adhesions	55 (22)	68 (35)	34 (34)	0.004
Uterolysis	2 (1)	11 (6)	2 (2)	0.01
Conversion to open	5 (2)	0 (0)	2 (2)	--

BS: Bilateral salpingectomy; BSO: Bilateral salpingo-oophorectomy; SC: Sacrocolpopexy; LAVH: Laparoscopic assisted vaginal hysterectomy; LSH: Laparoscopic supracervical hysterectomy; RATLH: Robotic-assisted laparoscopic hysterectomy; TLH: Total laparoscopic hysterectomy; USLS: Uterosacral ligament suspension.

compared to five (2%) patients in the low-volume group were. When comparing high and low-volume surgeons, there was no statistically significant difference in urinary tract injury (1% *vs* 2%) or bowel injury (1% *vs* 0%). There were more complications in the low-volume group *vs* the high-volume group when looking at complications aside from urinary tract, bowel, or major vessel injury. High-volume surgeons had four (1%) patients with a complication and low-volume surgeons had 12 (4%) patients with a complication (P = 0.04). For high-volume surgeons, three patients had a postoperative wound infection or pelvic abscess, and one had a small bowel obstruction. For low-volume surgeons, four patients had vaginal cuff dehiscence, one patient had a small bowel obstruction, three patients required a blood transfusion postoperatively, one patient returned to the hospital with vaginal bleeding, and three patients had a postoperative wound infection or pelvic abscess.

DISCUSSION

We found no difference in the incidence of urinary tract injury when comparing subspecialists to general gynecologists or between high and low-volume surgeons. However, it is important to note that our study was underpowered, and therefore, a conclusion cannot be drawn. To our knowledge, this is the first study to look at differences in urinary tract injury rates in general gynecologists *vs* subspecialists. We plan to continue collecting data to gain a larger sample size to reach appropriate statistical power.

When comparing high and low-volume surgeons, low-volume surgeons had an increased rate of complications (excluding urinary tract injury and bowel injury) when compared to high-volume surgeons. This aligns with the findings of Rogo-Gupta *et al*[10], who reported that high-volume surgeons were less likely to have perioperative complications than low-volume surgeons. All high-volume surgeons in our study were subspecialists. As such, the increased incidence of complications

Table 4 Patient demographics of high *vs* low-volume surgeons, *n* (%)

	High-volume, *n* = 280, mean ± SD	Low-volume, *n* = 273, mean ± SD	*P* value
Age (yr)	58.1 ± 12.3	46.0 ± 8.8	< 0.0001
Race			
Black	60 (21)	93 (35)	0.002
White	197 (70)	161 (59)	
Other/Unknown	23 (8)	17 (6)	
BMI	30.9 ± 7.8	32.6 ± 7.8	0.01
Cardiovascular disease	92 (33)	46 (17)	< 0.0001
Hypertension	127 (45)	90 (33)	0.003
Diabetes mellitus	42 (15)	25 (9)	0.04
Chronic lung disease	41 (15)	46 (17)	0.49
History of abdominal surgery	153 (55)	171 (63)	0.06

BMI: Body mass index.

Table 5 Operating time of high *vs* low-volume surgeons

	High-volume, *n* = 280, mean ± SD	Low-volume, *n* = 273, mean ± SD	*P* value
Total set-up time (min)	47.5 ± 9.6	35.2 ± 9.3	< 0.0001
Total operating time (min)	224.4 ± 73.8	140.0 ± 62.7	< 0.0001
Total room time (min)	303.9 ± 82.1	200.3 ± 68.1	< 0.0001

seen in low-volume surgeons could be attributed to decreased surgical volume or lack of subspecialty training.

Limitations of this study include the inherent nature of a retrospective study and differences in surgical technique. This institution has only one urogynecologist and therefore these results cannot be generalized to results of all urogynecologists. There are also many physicians at this hospital that perform hysterectomies at multiple hospitals and, therefore, these procedures were not accounted for in this study. If the surgeries performed at other institutions were accounted for, there is a possibility that some of the generalists would qualify as high-volume surgeons.

Strengths of this study include a wide variety of general gynecologists and gynecologic oncologists to account for varied surgical technique and increased generalizability. All methods of minimally invasive hysterectomies are performed at this institution and therefore represented in this study. This study was also performed at a large institution in an urban city further increasing the generalizability. To our knowledge, this was the first study to look at differences in urinary tract injury rates in general gynecologists *vs* subspecialists. This study provides a guide for further and more widespread studies to be performed to investigate if a difference truly exists.

CONCLUSION

Surgeon volume has previously been shown to play a role in rate of urinary tract injury during minimally invasive hysterectomies. Although it has not been studied previously, it is reasonable to assume that this may also hold true for subspecialists *vs* general gynecologists, as subspecialists are usually high-volume surgeons. Our study demonstrated that there was no difference in the urinary tract injury rate in general gynecologists *vs* subspecialists, however our study was underpowered. We recommend a multicenter study to better analyze the potential differences.

ARTICLE HIGHLIGHTS

Research background

It is well known that urinary tract injury is a complication of hysterectomies. There have been many studies that aim to determine if surgeon volume has an impact on the incidence urinary tract injury during hysterectomies. However, no studies have compared subspecialists to general gynecologists when assessing the incidence of urinary tract injury.

Research motivation

Urinary tract injury increases morbidity for patients who undergo hysterectomy. Subspeciality training and surgeon volume are factors that should be assessed when determining the incidence of urinary tract injury in an effort to decrease patient morbidity.

Research objectives

Our primary outcome was the incidence of urinary tract injury between fellowship trained board-certified female pelvic medicine and reproductive surgery surgeon, fellowship trained board eligible or board-certified gynecologic oncology surgeons, and board-certified or board eligible general gynecologists. Our secondary outcome was the incidence of urinary tract injury between high (defined by 30 or more minimally invasive hysterectomies per year) and low-volume surgeons (defined by less than 30 hysterectomies per year).

Research methods

We conducted a retrospective chart review of adult patients who underwent minimally invasive hysterectomy. All patients who underwent the following surgeries with or without concomitant procedures were included: Laparoscopic supracervical hysterectomy, laparoscopic assisted vaginal hysterectomy, total laparoscopic hysterectomy, and robotic hysterectomy. After we identified eligible patients, the surgeon subspecialty was identified and the surgeon's volume per year was calculated. Univariable analysis of factors associated with surgeon type and ureteral injury were assessed using Student's *t*-test, ANOVA followed by multiple pairwise comparisons using the Bonferroni correction of the *P* value, and the χ^2 analysis. Non-parametric tests were performed for data that were non-normally distributed, such as the Mann-Whitney U test and Kruskal-Wallis test.

Research results

Urologic injury occurred in four patients (2%) in the general gynecologist group, in one patient (1%) in the gynecologic oncologist group, and in one patient (1%) in the urogynecologist group. Bowel injury occurred in three (3%) of patients in the gynecologic oncologist group and there were none in the general gynecologist and urogynecologist groups. There were no cases of major vessel injury.

Research conclusions

When comparing high and low-volume surgeons, there was no statistically significant difference in urinary tract injury (1% *vs* 2%) or bowel injury (1% *vs* 0%). There were more complications in the low-volume group *vs* the high-volume group when looking at complications aside from urinary tract, bowel, or major vessel injury.

Research perspectives

To our knowledge, this was the first study to look at differences in urinary tract injury rates in general gynecologists *vs* subspecialists. This study provides a guide for further and more widespread studies to be performed to investigate if a difference truly exists.

FOOTNOTES

Author contributions: Khair EL designed the study, collected data, and wrote and edited the manuscript; Afzal F, Kulkarni SP, and Duhe' BJ collected data for the manuscript; Hagglund K analyzed the data for the manuscript; Aslam MF edited the manuscript and assisted in study design; All authors have read and approved the final manuscript.

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LETTER TO THE EDITOR

Sexual function history taking in medicine

Raktim Swarnakar, Shiv Lal Yadav

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Abstract

Sexual history taking is important for the proper diagnosis and treatment of sexual dysfunction. It is often neglected in a clinical setting and it is also underreported by patients due to stigma and hesitation. Here we have described how we should take sexual function history taking during any sexual dysfunction.

Key Words: Sexual function; Sexual dysfunction; History taking; Medicine; Rehabilitation medicine

Core Tip: Sexual history taking is crucial for the diagnosis and management of sexual dysfunction. It is often neglected in a clinical setting and it is also underreported by patients due to stigma and hesitation. Here we have highlighted how we should take sexual function history taking during any sexual dysfunction.

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TO THE EDITOR

Reproduction is a basic feature of living organisms for continuing their own species. Sexual function is vital for reproduction in this process[1]. Unfortunately, it is often neglected[2]. Especially sexual dysfunctions are often neglected as a medical condition [2]. It is also not thoroughly taught during the undergraduate medical curriculum and also during the postgraduate medical study[3]. Here we have highlighted how we should take sexual function history taking during any sexual dysfunction.

Sex

It refers to biological features that define as male or female, *etc*[4].

Sexual health

'Sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence. For sexual health to be attained and maintained, the sexual rights of all persons must be respected, protected and fulfilled'[4].

Sexuality

'A central aspect of being human throughout life encompasses sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy and reproduction. Sexuality is experienced and expressed in thoughts, fantasies, desires, beliefs, attitudes, values, behaviours, practices, roles and relationships'[4].

Fertility

It is the capability to produce offspring through reproduction after sexual maturity. Infertility can be caused by a variety of conditions. Mishra *et al*[5] interestingly described that mild oxidative stress is beneficial but severe oxidative stress is harmful to male fertility. Hence any clinical condition leading to 'stress' must be addressed with priority in history taking.

Barriers

It is considered taboo in many areas in spite of its importance; no definite sex education exists especially in India or many countries; patient underreports his/her sexual problems to physicians due to stigma or taboo or hesitation; no specific guidelines for sexual history taking in the basic medical curriculum. Studies showed sexual history is taken as low as only 8% of cases at the clinical visit[6].

Overall comprehensive male and female sexual rehabilitation is taken care of under the Physical Medicine and Rehabilitation domain. Since rehabilitation medicine aims at the functional status improvement of patients, sexual function improvement is an important domain here. Furthermore, it is of utmost importance for primary care physicians as well.

STEPS OF SEXUAL HISTORY TAKING

There are multiple models are followed for sexual history taking: ALLOW (ask, legitimize, limitations, open discussion, work together), PLISSIT (permission, limited information, specific suggestions, intensive therapy) and BETTER (bring up, explanation, tell, time, educate, record) models[7-9]. (1) Make the patient comfortable before you go on asking private questions. Ask for permission or consent; (2) Initially use gender-neutral terms (spouse, better-half, partner *etc.* instead of girlfriend or boyfriend or husband-wife); (3) Then, ask in what gender patient wants to identify him/her *etc.* Is he/she comfortable with his/her gender? (4) Ask for the sexual orientation of the person, and decide whether the person is asexual, bisexual, heterosexual, or homosexual; (5) For males: Ask for psychogenic, reflexogenic erection. Ask for ejaculation (premature/delayed) and orgasm (absent, reduced/altered, normal), questions regarding scrotal hygiene/scrotal functioning/pain *etc*; (6) For females: Ask for psychogenic, reflexogenic genital arousal, genito-pelvic pain and menstruation. Also ask regarding pregnancy related history; (7) Check the quality of life by specific measurement scales [Emotional Quality of the Relationship Scale, Female Sexual Function Index, Sexual Attitude and Information Questionnaire, *etc.*]. Check how much it has been affected by sexual dysfunction; (8) Check the reason for dysfunction by history and examination; (9) Medical history to exclude medical causes of sexual dysfunction (cardiovascular disorder, diabetes, sexually transmitted disease, endocrine dysfunction, prostate dysfunction, spinal cord disorder/injury, brain injury/disorder *etc.*); (10) Fertility is an important domain that needs to be addressed in history, conditions that lead to 'stress' can influence fertility, especially in male[5]; (11) Medicine or substance abuse history: Antipsychotics, alcohol, recreational drugs *etc*; (12) Psychiatric disorders like depression/anxiety, post-traumatic stress disorder *etc*; (13) Relationship status with partner; and (14) Check 5 Ps (Partners, Practices, Protection from STIs, Past History of STIs and Pregnancy Intention)[10].

Thus, history should direct to identify the root cause so that further clinical examination and investigations can be proceeded.

FOOTNOTES

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