Review article

Minimally-invasive parathyroid surgery

Chirurgia paratiroidea mini-invasiva

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SUMMARY

During the last two decades, several techniques for minimally-invasive parathyroidectomy have been developed, including open approaches (open minimally-invasive parathyroidectomy – OMIP), minimally-invasive radio-guided parathyroidectomy (MI-RP), video-assisted parathyroidectomy (VAP), video-assisted parathyroidectomy through a lateral approach (VAP-LA) and purely endoscopic parathyroidectomy (EP). We have reviewed the pertinent literature, analyzing the indications, outcomes, advantages and disadvantages of the different techniques. Even if the field of minimally-invasive parathyroidectomy is heterogeneous, there is some evidence that minimally-invasive video-assisted parathyroidectomy (MIVAP) should be preferred over OMIP for better cosmetic outcomes, improved visualization of neck structures and control of pain. There is also low-level evidence that MIVAP has some advantages over other purely endoscopic procedures for parathyroidectomy and VAP-LA, in terms of technical difficulties, in addition to the possibility to perform bilateral exploration and associated procedures on the thyroid gland. While the data on medium-term results are encouraging, longer follow-up times are still needed to confirm its safety and rate of cure with respect to conventional surgery. It has been demonstrated that MIVAP is also feasible in secondary and familial hyperparathyroidism, although no conclusive data are available.

KEY WORDS: Minimally invasive parathyroidectomy • Endoscopic parathyroidectomy • Video-assisted parathyroidectomy

RIASSUNTO

Nel corso degli ultimi due decenni sono state sviluppate e descritte numerose tecniche di paratiroidectomia mini-invasiva, che comprendono gli approcci cosiddetti "aperti" (Open Minimally Invasive Parathyroidectomy – OMIP), la paratiroidectomia mini-invasiva radioguidata (Minimally Invasive Radio-guided Parathyroidectomy – MI-RP), la paratiroidectomia video-assistita (Video-Assisted Parathyroidectomy – VAP), la paratiroidectomia video-assistita con approccio laterale (Video-Assisted Parathyroidectomy by lateral approach – VAP-LA) e le tecniche puramente endoscopiche (Endoscopic Parathyroidectomy – EP). In questo lavoro abbiamo valutato la letteratura, analizzando per le varie tecniche le indicazioni, i risultati, i vantaggi e gli svantaggi. Dall'analisi della letteratura, in un campo così eterogeneo come quello della paratiroidectomia mini-invasiva, si evince come esistano evidenze che fanno preferire la MIVAP alla OMIP, in ragione del miglior risultato estetico, della migliore visualizzazione delle strutture cervicali e del minor dolore postoperatorio. Ci sono inoltre delle evidenze, anche se di basso livello, che mostrano dei vantaggi della MIVAP sulle altre tecniche endoscopiche e sulla VAP-LA in termini di minori difficoltà tecniche, possibilità di effettuare un'esplorazione bilaterale e procedure associate sulla tiroide. Sebbene i risultati a medio termine siano entusiastici, è necessario un follow-up più lungo per confermarne l'efficacia in termini di tasso di guarigione rispetto alla chirurgia convenzionale. Recentemente la MIVAP è stata proposta anche per il trattamento dell'iperparatiroidismo secondario e familiare, ma ad oggi non sono disponibili dati conclusivi.

PAROLE CHIAVE: *Paratiroidectomia mini-invasiva • Paratiroidectomia endoscopica • Paratiroidectomia video-assistita*

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Introduction

Bilateral neck exploration (BNE) with the identification of at least four parathyroid glands and removal of pathological parathyroid tissue has for several decades represented the standard of treatment of primary hyperparathyroidism (pHPT) [1]. In experienced hands, this approach has a cure rate of more than 95% with minimal morbidity, which is usually less than 3% [1].

In spite of the excellent results obtained with BNE, since the early 1980s less invasive procedures (i.e. unilateral neck exploration, UNE) have been introduced, with the aim to reduce surgical trauma and the already low complication rate of parathyroidectomy [2 3]. The rationale stems from the fact that most patients (> 85%) with pHPT have a single parathyroid adenoma that is potentially identifiable and removable with selective cervical exploration. The application of minimally-invasive parathyroidectomy was initially limited. It was only during the last two decades that these procedures were widely developed because of improvements in preoperative localization techniques (ultrasound, sestaMIBI scintiscan) [4] and the introduction of a rapid intraoperative PTH (IO-PTH) assay [5]. In reality, if preoperative localization studies allow for a more targeted approach, the IO-PTH assay is able to intraoperatively confirm the success of surgery [6].

Indeed, in case of concordant ultrasonography and scintigraphy the overall accuracy in parathyroid localization is greater than 95%, while in cases of negative localization the likelihood of multiglandular disease (MGD) is more than 30% [7 8]. Obviously, the availability of accurate preoperative localization studies provides the opportunity to plan minimally-invasive surgical procedures aimed at removal of the affected gland(s) identified.
Similar to the progresses in the field of preoperative imaging techniques that allowed targeted approaches, the development and availability of the IO-PTH assay gave the opportunity to intraoperatively verify the completeness of surgical resection as an alternative to the complete visualization of all four glands [5 6 9-11]. Since rapid techniques for iPTH have been developed, the IO-PTH assay is an attractive method to intraoperatively verify the success of surgical resection, providing a "biochemical" frozen section.
While there are still some controversial aspects, especially in terms of cost-effectiveness and interpretation criteria, IO-PTH has emerged has a very useful intraoperative adjunct for parathyroidectomy, especially in cases of targeted parathyroidectomy relying on a single preoperative localization study, in those with discordant localization studies and in reoperative parathyroidectomy [12-16].

Minimally-invasive parathyroidectomy

The application of endoscopic techniques in neck surgery during the late 1990s determined a further impulse towards the development of minimally-invasive techniques for parathyroidectomy [17]. The general trend towards less invasive procedures for parathyroidectomy is well demonstrated by the results of an international survey among the members of the International Association of Endocrine Surgeons (IAES) where 59% of participants used a minimally-invasive approach [18]. It is likely that this percentage has further increased during the last decade.
Even if a minority of the authors consider standard BNE performed by an experienced endocrine surgeons as the best treatment for patients with pHPT [19], others retain that BNE should now be confined and to historical surgical textbooks [20].
Besides these extreme and provocative positions, minimally-invasive procedures for parathyroidectomy are assuming an increasingly important role, and are close to becoming the new gold standard for treatment of primary hyperparathyroidism, at least in its sporadic form.
The recently published consensus statement of the European Society of Endocrine Surgeons (ESES) assumed that even if BNE has excellent results and is always an option for the surgical treatment of pHPT, minimally-invasive parathyroidectomy is a safe and cost-effective procedure to treat selected patients with sporadic primary HPT, especially in the case of positive preoperative localization tests [13]. Similarly, the proceedings of the Third International Workshop on primary hyperparathyroidism reported that "unlike previous dogma that mandated surgical identification of both pathologically enlarged and normal parathyroid glands, the current paradigm in many centres is to identify and excise the incident enlarged gland and to confirm operative cure employing a rapid intraoperative PTH assay" [16]. On the other hand, an audit from the Scandinavian quality register for parathyroid surgery showed that BNE is still performed in two-thirds of parathyroid procedures [21]. Indeed, it is true that not all patients with hyperparathyroidism can be treated by a selective minimally invasive approach. Thus, BNE still maintains a relevant role in the treatment of patients with pHPT.
Minimally-invasive (focused, targeted or selective) parathyroidectomy encompasses a number of different techniques, including open approaches (open minimally-invasive parathyroidectomy, OMIP) [22 23], minimally-invasive radio-guided parathyroidectomy (MI-RP) [24], video-assisted parathyroidectomy (VAP) [25-27] and purely endoscopic parathyroidectomy (EP) [17 28-32]. As a consequence, there is no strict or unequivocal definition of what minimally-invasive parathyroidectomy (MIP) actually is. The term "minimally-invasive" should be reserved to a procedure that allows the surgeon to perform a traditional operation through an access that minimizes the trauma of surgical exposure and dissection. Considering an intervention such as BNE, which is associated with a very low morbidity (< 3%) and high success (> 95%) rates in the hands of experienced surgeons, a minimally-invasive procedure should obtain at least the same results, with the main advantage of reducing the invasive trauma and, consequently, allowing better cosmetic results [33]. MIP is indicated for parathyroid procedures performed through a small incision, usually less than 2.5-3 cm [33]. In other words, minimally-invasive should be involve a mini-incision or mini-access parathyroid procedures.
This definition is at least reductive, since mini-access does not mean necessarily a minimally-invasive procedure. Moreover, there are several other potential advantages of targeted parathyroid procedures (i.e. decreased postoperative pain and complications), which should be mainly related to less extensive surgical dissection. The curative outcomes should be at least the same as for BNE.
Indeed, several reports have demonstrated the feasibility of the concept of MIP or focused parathyroidectomy or selective parathyroidectomy. Most of these studies suggest that these focused techniques are safe and at least as good as standard BNE, with some advantages, especially in terms of less postoperative hypocalcaemia, shorter operative time, earlier discharge, better cosmetic results and reduced postoperative pain.

Techniques for MIP

Several variants of minimally-invasive procedures have been described over the last 15 years.

Minimally-invasive radio-guided parathyroidectomy – In MI-RP a handheld gamma probe is used to facilitate intraoperative localization, identification and dissection of the pathologic gland(s), and to confirm removal of all hyperfunctioning parathyroid tissue [24]. This approach necessitates IV injection of technetium-99m sestamibi 2-4 hours prior to surgery. Obviously, a prerequisite for this approach is the precise coordination between the operating room, nuclear medicine department, the surgeon and the nuclear medicine radiologist so that everything is timed correctly. The neck of the patients is scanned on the operating table and the site with highest counts is explored. An excised parathyroid adenoma should contain more than 20% of the post-excision background radioactivity [34]. This approach may result in reduced operative time [34] and eliminate the need for IO-PTH [24]. Although this technique has been refined and validated, it has been adopted only by a minority of endocrine surgeons worldwide, mainly because of the logistic requirements. Moreover, in some experiences utilization of the gamma probe was potentially misleading [35]. At present, MI-RP is considered an alternative minimally-invasive technique, with potential advantages in reoperative cases [12].

Open Minimally-Invasive Parathyroidectomy – OMIP is the most commonly used minimally-invasive technique [18 36]. A focused parathyroidectomy, performed through a small (2.5-5 cm) central [16] or lateral (over the site of the adenoma and overlying the anterior border of the sternocleidomastoid muscle) [23] incision, guided by preoperative localization studies, bedside surgeon performed ultrasonography and IOPTH, is the most attractive and widely-utilized technique for the surgical treatment of pHPT [6 16 18 22 23 37 38]. Indeed, it appears easy to learn and reproduce in different surgical settings, it can be performed under loco-regional anaesthesia, with reduced operative time and as a short stay procedure [6 37]. The main limitation of the different OMIP techniques resides in the potentially poor visualization of neck structures, due to the small size of the skin incision, or conversely, the need for larger skin incision when compared with video-assisted and/or endoscopic techniques. Since coexistent thyroid nodular disease is relatively common, associated thyroid resection can also be performed [38].

Video-assisted and endoscopic techniques – Procedures that imply the utilization of the endoscope (purely endoscopic and video-assisted techniques) take advantage not only of the targeted approach, but also of the endoscopic magnification that allows performing the same intervention through very minimal access(es). This is a theoretically associated with a lower risk of complications due to optimal visualization of neck structures (in particular the recurrent laryngeal nerve and parathyroid glands). Video-assisted and/or endoscopic techniques should be preferred mainly because of this important advantage, even if they require dedicated surgical instrumentation, an adequate and relatively prolonged learning curve and usually general anaesthesia. Nonetheless, at least from a theoretical point of view, endoscopic and/or video-assisted procedures are particularly suitable for parathyroid surgery, since they employ an ablative procedure for a benign disease.

Techniques utilizing an endoscope can be classified into endoscopic [28-32] and video-assisted procedures [25-27 39].

Endoscopic parathyroidectomy – Total EP was first described by Gagner in 1996 [17], and subsequently utilized, even if modified, by other authors [28 29]. It is carried out entirely under a steady gas flow, using a 5 mm endoscope introduced through a central trocar, and two or three additional trocars for needlescopic instruments. The dissection is first performed beneath the platysma to obtain a good working space. The midline is then opened and the strap muscles are retracted to expose the thyroid lobe and explore the parathyroid glands after dissecting the thyroid from the fascia.

Besides this technique, which employs cervical access, other procedures with an extracervical endoscopic approach have been described. These approaches gained initial success mainly in the Asian surgical community, where avoiding any neck scar seems to have utmost importance. Several approaches have been described, including extracervical accesses from the chest wall [30], breast [40] and axilla [41].

All endoscopic techniques are characterized by continuous CO_2 insufflation [17 28 29] or mechanical external retraction [32 41-43] to maintain the operative space for dissection and trocar positioning.

These procedures ensure optimal cosmetic results due to nearly invisible scars, but are difficult to be reproduced in different settings, especially by unskilled endoscopic surgeons, as they are technically demanding. Moreover, total endoscopic techniques with extracervical accesses, in order to further improve cosmetic outcome, require extensive and difficult dissection to reach the operation site through extracervical access, increasing the risk of complications and the invasiveness of the procedure. The lengthy operative time is another major limitation that has limited the diffusion of these approaches. Moreover, the risks related to CO_2 absorption are not completely eliminated [44].

Video-assisted parathyroidectomy by the lateral approach (VAP-LA) – VAP-LA was firstly described by Henry et al. [26]. The lateral approach is characterized by a 12 mm skin incision on the anterior border of the sternocleidomastoid muscle, 3-4 cm above the sternal notch on the side of the affected gland. Through this incision, the tissue is dissected with an open technique to reach the prevertebral fascia. Once enough space has been created, two 2.5 mm trocars are inserted on the line of the anterior border of the sternocleidomastoid muscle 3-4 cm above and below the first incision through which a 10 mm trocar for

the endoscope (10 mm, 0°) is inserted. Unilateral video-assisted parathyroid exploration and dissection is carried out with 8 mmHg carbon dioxide insufflation during the entire procedure. At the beginning of the experience with this approach, the operation was video-assisted [26 45]. Indeed, after dissection of the adenoma, the trocars were removed and the vascular pedicle was ligated and cut under direct vision, and the procedure was terminated under direct vision. After the initial learning curve, dissection was completely carried out under endoscopic vision [46 47]. After completing the dissection of the affected gland, small adenomas are directly extracted through the 10 mm trocar; large adenomas that cannot be introduced into the 10 mm trocar are extracted through the trocar site, under direct vision.

In the largest retrospective series reported [46], VAP-LA provided optimal visualization of neck structures, and was particularly suitable for adenomas deeply located in the neck or in the upper and posterior mediastinum, usually affecting the superior parathyroid gland. VAP-LA appeared to be highly reproducible. It allowed for a 99% cure rate, and was safe, with a minimal complication rate. Nonetheless, the rate of contraindications for VAP-LA was higher (43% *vs.* 29%) than for MIVAP. This is related to the eligibility criteria that include no evidence of nodular goitre and the strong demonstration of a single enlarged parathyroid gland on preoperative imaging studies.

In a series evaluating medium-term results of VAP-LA, Maweja et al. [47] reported a cure rate of 98.5% with 1 case of recurrent disease in 394 endoscopic procedures after a median follow-up of 20.5 months.

The main technical limitation of the technique is the unilateral approach that prevents the possibility to accomplish bilateral exploration when necessary without converting to an open conventional procedure.

Minimally-invasive video-assisted parathyroidectomy (MIVAP) – MIVAP was firstly described by Miccoli et al. [25] and in 1998 was adopted in our Department [27]. Early after its first description, the technique was widely accepted worldwide [48], likely as it is easily reproduced in different surgical settings. In reality, it reproduces in all the steps a conventional operation, and the endoscope is only a tool that permits the same operation through a smaller skin incision.

Indications for MIVAP – Ideal candidates for MIVAP are patients with sporadic pHPT in whom a single adenoma is suspected basing on preoperative MIBI-scan and ultrasonography. Parathyroid adenomas larger than 3 cm in their maximum diameter should not be selected for MIVAP, because of difficult dissection that can determine a dangerous capsular rupture and consequent parathyromatosis [49]. Exclusion criteria include previous conventional neck surgery, persistent or recurrent hyperparathyroidism, mediastinal adenomas or concomitant large goitre.

With increasing experience, selection criteria for MIVAP have been refined and widened. Patients with concomitant nodular goitre requiring surgical removal can be selected for MIVAP if the inclusion criteria for video-assisted thyroidectomy are respected [27]. In selected cases, patients with previous contralateral neck surgery or intrathymic/retrosternal adenomas can be selected for MIVAP. In case of suspected MGD, a video-assisted bilateral exploration can be planned [49]. Previous contralateral neck surgery (i.e. contralateral thyroid lobectomy) is no longer an absolute contraindication for MIVAP. In such cases, however, a lateral approach is preferable as it avoids the scar and fibrotic tissue consequent to the previous operation [49].

The percentage of patients with sporadic pHPT who are candidates for MIVAP has been reported to be highly variable (37-71%) [27 49], and it is mainly related to the different incidence of coexisting thyroid disease that may require a conventional approach [27].

Recently, MIVAP has also been proposed for patients with four hyperplastic glands (i.e. familial pHPT [50] and secondary and tertiary HPT) [50 51]. However, these latter indications should be still confirmed and validated by larger series and comparative studies.

MIVAP: Surgical procedure – The operative technique has been previously described in detail [52]. The patient, under general or loco-regional anaesthesia with cervical block, is positioned in a supine position with the neck in slight extension. The surgical team is composed of the surgeons and two assistants, one of whom handles the endoscope. The need for at least three surgeons has been considered to be one of the main limitations of this approach [27].

A small (1.5-2.0 cm) skin incision is performed between the cricoid cartilage and the sternal notch, in the midline. The skin incision is usually higher than in conventional cervicotomy and can also be modulated on the basis of the preoperative ultrasound findings. The thyroid lobe is separated from the strap muscles with small conventional retractors (Farabeuf retractors), which are also used to maintain the operative space. With this purpose, the thyroid lobe is medially retracted while the strap muscles on the affected side are retracted laterally. At this point, the endoscope (5 mm, 30°) and the small surgical instruments are introduced through the single skin incision without using any trocar. The endoscope is held in position with both hands by the assistant. This is accomplished with some difficulties. However, the absence of any external support allows changing the position of the endoscope in relationship to the particular needs of the dissection. This represents an important advantage of a video-assisted procedure over purely endoscopic techniques.

The first step of the procedure consists in complete freeing of the thyroid gland from the strap muscles, in order to have good exposition of the parathyroid sites. After identifying the inferior laryngeal nerve in the involved side, a targeted exploration is usually carried out to identify the abnormal gland that was localized preoperatively. In case of suspicion of multiglandular disease because of inad-

equate iPTH decrease or double gland enlargement at unilateral exploration, or in the case of inadequate preoperative localization studies, bilateral parathyroid exploration can be performed by the same video-assisted technique through the single, central skin incision. After identification, the affected parathyroid gland is bluntly dissected under endoscopic vision by using dedicated spatulas and a spatula shaped aspirator. The pedicle of the adenoma is usually clipped with titanium clips or ligated with conventional ligature. After cutting the pedicle, the adenoma is extracted through the skin incision. IO-PTH assay should confirm the removal of all pathologic tissue.

Results of MIVAP – The conversion rate is highly variable, ranging from 0.9% [27] to 43% [53]. The reasons for these differences are usually related to the difficulty in identification of the diseased gland(s), challenging dissection eventually related to suspicion of malignancy, suspicion of multiglandular disease or, eventually, false negative IO-PTH results or ectopic localizations. Nonetheless, one should consider that proper patient selection and the experience of the surgical team play an important role in the conversion rate.

Operative time is largely influenced by the skill of the surgical team, and the learning curve should be taken into account [54]. However, with increasing experience operative time decreases significantly and is comparable or even shorter to that of a conventional procedure [27 54].

Several large retrospective series have reported on outcomes and the medium term results of MIVAP. In a publication on 350 cases of MIVAP after six years of experience, Miccoli et al. [49] reported a cure rate of 98.3%. After a medium follow-up of 35.1 months, persistent disease was seen in 4 cases which were all due to false-positive results of IOPTH that failed in recognizing MGD. In that series, complications occurred in 14 patients. The authors reported 2.7% of transient hypocalcaemia, 0.8% definitive nerve palsy (3 cases) and 0.3% postoperative bleeding. In our published series of 107 cases of video-assisted parathyroidectomy with central access, we reported a similar success rate of 98.1% with persistent disease in 2 cases (1.9%) [27]. We observed a higher rate (11.1%) of temporary hypocalcaemia, with no cases of definitive hypoparathyroidism, while no other complications were observed [27].

However, long-term results evaluating recurrent disease rate have not been reported.

Advantages and disadvantages of MIVAP – MIVAP gained a quite wide diffusion in several referral centres [27 48 55] shortly after its first description. The reasons of its success when compared with other techniques are due to a number of factors. First of all, it combines the advantages of endoscopic magnification with those of conventional surgery. This distinguishes it from other endoscopic techniques, which have an access that is completely different from conventional surgery. Nonetheless, a learning period should be taken into account [49 54]. The excellent visualization of neck structures due to the 2- to 3-fold endoscopic magnification permits easy and prompt identification of the laryngeal nerve and parathyroid glands, reducing the risk of nerve palsy or the troublesome occurrence of capsular gland rupture. In a recently published prospective randomised trial, the mean time for adenoma localization was significantly shorter in the group of patients who underwent MIVAP compared to those undergoing an open minimally-invasive technique (OMIP) [55].

Another merit of the technique is the possibility to perform bilateral neck exploration when necessary through the same central access. This characteristic in part explains the very low conversion rate reported in larger series (0.9-8%) [27 49]. The possibility to perform a bilateral neck exploration has two main effects on the restrictive inclusion criteria. Firstly, MIVAP can be performed in case of unavailability of intraoperative PTH monitoring or if preoperative localization studies are inadequate [27 39 56]. A recently published prospective randomised study [56] compared bilateral video-assisted neck exploration after the removal of enlarged glands, and focused on MIVAP plus IO-PTH to evaluate the effectiveness of the two techniques in the treatment of patients with pHPT. It was reported that bilateral video-assisted neck exploration was as safe and effective as MIVAP with IO-PTH, and did not prolong the time of the surgical procedure.

Its low invasiveness and similarity with a conventional procedure render this approach feasible also under loco-regional anaesthesia (cervical block) [57], at least in selected patients, with the benefits of avoiding the major side effects of general anaesthesia. Moreover, it has been demonstrated that loco-regional anaesthesia allows for a significant reduction of operating room occupation time, and is associated with significantly less postoperative pain [57]. As for other targeted approaches, it can be performed on an outpatient basis and/or same day procedure, at least in selected cases.

Another advantage of central access is the possibility to associate it with thyroid resection, even bilateral, when necessary. This makes a important difference not only compared to other endoscopic techniques, but also to OMIP, since conversion to a conventional approach is usually required when bilateral thyroid resection is needed [24]. Because of the high prevalence of multinodular goitre in some countries, this technical characteristic allows experienced surgeons to increase the number of patients eligible for a video-assisted procedure [27 39]. In our experience, because of the high prevalence of goitre in Italy, this allows to treat both diseases during the same procedure in a significant percentage of patients (about 20%) [27].

Another important advantage over other endoscopic and non-endoscopic minimally-invasive techniques is that it allows thorough exploration of deeply located inferior pathologic glands (i.e. retrosternal, intrathymic). This is

because the endoscope is not limited in its position by any external device, and it can be rotated and placed in any direction, so that the entire neck and upper mediastinum trough can be explored through a very small skin incision.

Minimal access also provides better cosmetic results, and the absence of neck hyperextension and extensive dissections may result in less postoperative pain. Indeed, several comparative studies have demonstrated the advantages of MIVAP in terms of reduced postoperative pain, better cosmetic results and higher patient satisfaction compared to both conventional and open non-endoscopic minimally-invasive parathyroidectomy [55 58].

Despite all these advantages and the excellent results in terms of complication and cure rates, as already noted, there are major concerns for the routine application of MIVAP in clinical practice due primarily to technical and economic aspects.

Firstly, the need for specific instrumentation for MIVAP has been considered a source of additional costs compared with conventional surgery. However, in almost all operating rooms endoscopic tools (endoscope, video, light source, camera, etc.) are now available. Moreover, the small specific instruments needed for MIVAP are reusable and costs are thus reduced accordingly.

Operative time, which was considered to be one of the limits of the technique, has been demonstrated to decrease with increasing experience and even to rival that of conventional surgery [49 54]. Moreover, small prospective randomised comparative studies showed that the operative time for MIVAP was significant shorter than conventional bilateral exploration [58] and similar to open minimally-invasive parathyroidectomy [55].

There is some criticism concerning the number of members of the surgical team. Indeed, two assistants are necessary to accomplish the procedure, since one must hold the endoscope. This can be an important problem for its application in all surgical settings.

On the other hand, the possibility to perform the procedure under loco-regional anaesthesia, to carry out concomitant thyroid resection and to explore the entire neck, have recently extended the indications for MIVAP. However, they are still limited since not all patients are eligible for the procedure, especially in areas of endemic goitre, where a large thyroid gland can hinder video-assisted dissection. This is well represented in our experience, in an endemic goitre area, where only 37% of patients with sPHPT were eligible for VAP because of the presence, in the majority of cases, of large multinodular goitre, which required concomitant conventional thyroid resection [27].

At the beginning of the experience, another technical limitation for the procedure was previous neck surgery. With increasing experience, however, re-operative neck surgery was demonstrated to be feasible, and patients with contralateral thyroid resection were approached by MIVAP [27 49]. Another technical limitation concerns large parathyroid adenomas (> 30 mm). Indeed, dissection and extraction of large adenomas through a small incision can result in capsule rupture with the theoretical risk of parathyromatosis. Nonetheless, this complication has not been reported.

In summary, at present the main limitations of MIVAP are related to the parathyroid adenoma and goitre volume. In contrast, previous neck surgery and the absence of a clear preoperative localization should not still be considered absolute contraindications for this approach.

MIP: evidence-based recommendations

Four randomized trials comparing minimally-invasive open parathyroidectomy with standard BNE have been published [59 60]. These studies all demonstrated that unilateral neck exploration, under both general [59-61] and loco-regional anaesthesia [62], is associated with shorter operative time [59 62], and the same cure rate at short- [61] and long-term follow-up [60].

One prospective randomised trial compared MIVAP with BNE considering operative time, postoperative pain, complications, cosmetic results and cost [58]. The results showed a significant decrease in operative time, postoperative pain and postoperative inactivity period with MIVAP. Patient satisfaction for cosmetic outcome was significantly superior in the group of patients who underwent MIVAP. No significant differences between the two procedures were found in terms of overall costs [58].

A larger non-randomized case-control study with historical controls matched for age and sex by Henry et al. [45] compared the results of VAP-LA and BNE. Statistically significant advantages were seen in favour of the VAP-LA group considering analgesic requirements and patient satisfaction with cosmetic outcome.

On the basis of these five studies, MIP should be considered as an initial, safe and cost-effective surgical approach for the treatment of a proportion of patients with sporadic pHPT. Single-gland excision through limited, selective exploration does not imply an increased risk of persistent/recurrent pHPT compared to BNE. The prevalence and severity of postoperative hypocalcaemia appeared to be lowered by MIP [12].

Concerning the type of anaesthesia, one randomized clinical trial comparing regional and general anaesthesia for MIVAP has been published [57]. The results showed that, although operative time was similar in the two groups, the operative room occupation time (interval between induction of anaesthesia and return to the ward) was significantly less in case of loco-regional anaesthesia. Moreover, patients undergoing MIVAP required significantly less postoperative analgesics. No significant difference was found between the two groups in terms of the complication rate. Thus, there is evidence that MIVAP is feasible

under loco-regional anaesthesia with a shorter overall operative time and lower postoperative pain and analgesic consumption [57].

All types of focused parathyroidectomy rely on preoperative localization studies and IO-PTH monitoring. While some authors have recently questioned the utility of IO-PTH as "added value" to intraoperative decision-making, most agree that it is an important, even essential, complementary tool for a minimally-invasive procedure. In a retrospective non-randomised comparative study, Barczynski et al. [13] found that the routine use of IO-PTH significantly improved the cure rates of minimally-invasive open or video-assisted parathyroidectomy in comparison to open image-guided unilateral neck exploration without IO-PTH. Furthermore, IO-PTH offered an added value to the surgical decision of further neck exploration, especially in case of only one positive imaging study [13].

It is important to underline that MIVAP consents bilateral neck exploration without converting to open conventional surgery. This in theory would allow avoiding the use of IO-PTH. A randomised trial [56] has compared bilateral neck exploration to focused parathyroidectomy plus IOPTH during MIVAP to evaluate their effectiveness, outcomes, operative time and costs. It was seen that endoscopic bilateral exploration can be performed without the time and costs of IO-PTH, but with the same effectiveness of endoscopic focused parathyroidectomy with IO-PTH monitoring, without prolonging the surgical procedure. The major drawback of such an approach consists in the risk of unjustified removal of enlarged but non-pathologic parathyroid glands [56]. As a consequence, IO-PTH can be avoided if video-assisted BNE is performed.

Finally, two prospective randomized trials have compared the two most widely employed approaches for MIP, namely OMIP and MIVAP. In the first report by Barczyński et al. [55], the two minimally-invasive techniques showed similar results in both cure and morbidity rates, operative time, postoperative hospital stay and long-term satisfaction with cosmetic outcome. In the MIVAP group, easier recognition of the recurrent laryngeal nerve, significantly less pain during 24 hours following surgery, lower analgesic request rate and analgesic consumption and shorter scar length were observed. Moreover, the MIVAP group had significantly better physical functioning and a higher cosmetic satisfaction rate at 1 month after surgery. On the other hand, costs were significantly higher for MIVAP, due to the use of endoscopic tools. In a second multicentre trial, patients were randomized to an open or video-assisted approach, by either central or lateral access [53]. OMIP has shorter operation times than the video-assisted technique, while no significant difference was found in terms of postoperative outcomes. However, the main limitations of this study reside in its multicentre design and in the fact that at least some of the surgeons had not yet reached an adequate experience in video-assisted procedures at the time of the study. This could explain the high conversion rate in the video-assisted group (43%: 25% to BNE, 18% to OMIP), which would otherwise show a significant difference in operative time between the two groups [53].

Conclusions

In the heterogeneous field of minimally invasive parathyroidectomy, there is some evidence that MIVAP should be preferred over OMIP for better cosmetic outcomes, improved visualization of neck structures and pain control [63]. There is also some low-level evidence that MIVAP has some advantages over other purely endoscopic procedures for parathyroidectomy and VAP-LA, in terms of technical difficulties, and the possibility to perform bilateral exploration and associated procedures on the thyroid gland [63]. While the data on medium-term results are encouraging, longer follow-up times are needed to confirm its safety in term of cure rates with respect to conventional surgery. Lastly, MIVAP is also feasible in the case of secondary and familial hyperparathyroidism [50 51], although no conclusive data are available.

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