NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of phrenic nerve transfer in brachial plexus injury

Repairing damaged nerves after brachial plexus injury by transferring a nerve from the diaphragm

The brachial plexus is the bundle of nerves from the neck to the armpit which supplies movement and feeling to the arm and hand. Damage to the brachial plexus can cause paralysis of the arm or hand, and can be associated with severe pain.

This procedure uses the phrenic nerve (the nerve to the diaphragm – a muscle in the bottom of the ribcage that is used for breathing) to repair damaged nerves in the brachial plexus, with the aim of restoring some useful function to the arm.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in December 2012.

Procedure name

- Phrenic nerve transfer in brachial plexus injury

Specialist societies

- British Orthopaedic Association
- British Association of Plastic Reconstructive and Aesthetic Surgeons (BAPRAS)
- British Thoracic Society.

Description

Indications and current treatment

Brachial plexus injuries are typically caused by traction of the arm at birth and by road traffic accidents. They result in loss of sensation and movement in all or part of the arm and can be associated with severe pain. The exact symptoms depend on the severity and location of the injury.

Brachial plexus injuries in which the nerves are injured but still intact are usually managed by conservative care, including physiotherapy. If the plexus has been disrupted then surgical repair is considered. This may be possible by direct suture, or it may involve the use of nerve grafts if the nerve ends are separated. If neither of these is possible, for example in nerve root avulsion, nerve transfer (neurotisation) can be done, in which a healthy nerve to a different muscle is joined to a damaged nerve, to re-innervate the affected arm muscle. A variety of nerves may be used for this kind of procedure, including intercostal nerves, the spinal accessory nerve, the phrenic nerve and the motor branches of the cervical plexus. Sometimes, free muscle or tendon transfer is done in combination with nerve transfer to re-innervate the forearm muscles.

What the procedure involves

The procedure is performed under general anaesthesia, by a supraclavicular approach. The brachial plexus is explored and the root avulsion confirmed. The phrenic nerve is identified in the neck on the surface of the scalenus anterior muscle, or in the chest thorascopically to provide a longer segment for grafting. Phrenic nerve function is confirmed by neurophysiology. The nerve is divided, transferred and joined to the distal segment of the selected damaged nerve either directly or via an interposition graft if necessary. The aim of the procedure is to re-innervate the target muscles and improve upper limb function.

Postoperatively, a head and shoulder spica may be applied for several weeks to avoid tension on the nerve transfer. Specialist rehabilitation is provided to maximise the recovery of useful arm function.

Phrenic nerve transfer may be combined with other donor nerve transfers at the same time or in stages.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to phrenic nerve transfer in brachial plexus injury. Searches were conducted of the following databases, covering the period from their commencement to 12 December 2012: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	**Criteria**
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with brachial plexus injuries.
Intervention/test	Phrenic nerve transfer.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on 229 patients from 1 quasi-randomised study, 1 retrospective comparative study, 2 prospective case series and 4 retrospective case series.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on phrenic nerve transfer in brachial plexus injury

<table>
<tr><td colspan="4">Abbreviations used: ABPI, avulsed brachial plexus injuries; BPI, brachial plexus injury; CXR, chest fluoroscopy; DLCO, single breath diffusing capacity of the lung for carbon monoxide; FRC, functional residual capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; ICNT, intercostal nerve transfer; IC, inspiratory capacity; MCN, musculocutaneous nerve; MIT, multiple intercostal nerve transfer; MRC, medical research council; MVV, maximum ventilation volume; PFTs, pulmonary function tests; PNT, phrenic nerve transfer; RV, residual volume; SAN, spinal accessory nerve; SD, standard deviation; TV, tidal volume; TLC, total lung capacity; VC, vital capacity; Vo_2, oxygen uptake.</td></tr>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Chalidapong P (2004)[1]

Quasi-randomised comparative study
Thailand
Recruitment period: 1998–2000
Study population: BPI patients with nerve root avulsions
n=36 (17 PNT vs 19 ICNT)
Age: mean 25 years
Sex: 92% (33/36) male

Patient selection criteria: aged 13 or over with a complete nerve root avulsion type of BPI needing neurotisation.
Exclusion criteria: evidence of diaphragmatic paralysis, history of chest trauma, fractures or biceps muscle injuries to the same arm, unable to return to follow-up.
Time interval from injury to surgery: less than 6 months.

Technique: a single surgeon performed nerve transfers using either the third or fourth ICNs or the phrenic nerve to MCN. All PNTs needed a sural nerve graft. Preoperatively, all patients underwent physical examinations, chest X-rays for detection of diaphragmatic paralysis, electro diagnostic studies and PFTs using autospiropal spirometer. Postoperatively,</td>
<td>Number of patients analysed: (17 PNT vs 19 ICNT)

Biceps function
Time to first observation of a biceps contraction
Patients in the ICNT group had significantly earlier recovery of biceps contraction (mean 195 days; range 131–330) (p=0.03) than those in the PNT group (mean 262 days; range 166–540).

Biceps recovery at 1 year after PNT and ICNT
Motor recovery to MRC grade 3 or more in the biceps muscle was observed in 53% (10/19) of patients in the ICNT group and 29% (5/17) of patients in the PNT group. Four patients in the PNT group had no recovery of biceps muscle at 1 year, but all the patients in the ICNT group regained some motor function in muscle and, after rehabilitation, could separate breathing from biceps function.</td>
<td>Comparison of reduction in pulmonary function between and within PNT and ICNT groups
<table>
<tr><th>PF measures</th><th>ICNT group (n=19) Mean % differences ± SD</th><th>PNT group (n=17) Mean % differences ± SD</th><th>p-value</th></tr>
<tr><td colspan="4">FVC (pre-op value identical for each group (3.2±0.7))</td></tr>
<tr><td>2 weeks
p-value*</td><td>7±10
0.005</td><td>20±9
<0.001</td><td>0.001</td></tr>
<tr><td>6 months
p-value*</td><td>1±5
ns</td><td>18±14
<0.001</td><td><0.001</td></tr>
<tr><td>12 months
p-value*</td><td>-2±3
0.017</td><td>6±5
<0.001</td><td><0.001</td></tr>
<tr><td colspan="4">FEV1 (pre-op value identical for each group (2.9±0.6))</td></tr>
<tr><td>2 weeks
p-value*</td><td>9±13
0.004</td><td>19±11
<0.001</td><td>0.015</td></tr>
<tr><td>6 months
p-value*</td><td>2±5
0.036</td><td>19±15
<0.001</td><td><0.001</td></tr>
<tr><td>12 months
p-value*</td><td>-1±4
ns</td><td>6±7
0.003</td><td>0.001</td></tr>
<tr><td colspan="4">VC (pre-op value identical for each group (3.1±0.7))</td></tr>
<tr><td>2 weeks
p-value*</td><td>6±11
0.029</td><td>21±9
<0.001</td><td><0.001</td></tr>
<tr><td>6 months</td><td>0±8</td><td>18±16</td><td><0.001</td></tr>
</table>
</td>
<td>Follow-up issues:
• Complete follow-up
Study design issues:
• Single-centre study
• Patients were recruited consecutively and were assigned by alternating between groups by the date of admission (odd vs. even dates).
• Nerve grafts were not needed for the ICN transfer.
Study population issues:
• There were no statistically significant differences in the baseline characteristics of the ICN and PNT groups</td>
</tr>
</table>

<table>
<tr><td colspan="4">Abbreviations used: ABPI, avulsed brachial plexus injuries; BPI, brachial plexus injury; CXR, chest fluoroscopy; DLCO, single breath diffusing capacity of the lung for carbon monoxide; FRC, functional residual capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; ICNT, intercostal nerve transfer; IC, inspiratory capacity; MCN, musculocutaneous nerve; MIT, multiple intercostal nerve transfer; MRC, medical research council; MVV, maximum ventilation volume; PFTs, pulmonary function tests; PNT, phrenic nerve transfer; RV, residual volume; SAN, spinal accessory nerve; SD, standard deviation; TV, tidal volume; TLC, total lung capacity; VC, vital capacity; Vo_2, oxygen uptake.</td></tr>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>every 3 months, PFTs were performed by measuring FVC, FEV1, VC, and TV. The effect of body position on FVC was also recorded by comparing the FVC in standing and supine positions. The time to recovery of first biceps contraction and biceps power during the first year after surgery were recorded. Motor recovery of biceps was serially recorded.

Follow-up: 12 months

Conflict of interest/source of funding: not reported.</td>
<td></td>
<td>
<table>
<tr><td>p-value*</td><td>ns</td><td><0.001</td><td></td></tr>
<tr><td>12 months
p-value*</td><td>-3±6
ns</td><td>8±8
<0.001</td><td><0.001</td></tr>
<tr><td colspan="4">TV (pre-op value NS (1.0±0.3 ICNT; 0.9±0.2 PNT)</td></tr>
<tr><td>2 weeks
p-value*</td><td>11±24
0.040</td><td>22±19
<0.001</td><td>0.137</td></tr>
<tr><td>6 months
p-value*</td><td>12±10
<0.001</td><td>30±22
<0.001</td><td>0.002</td></tr>
<tr><td>12 months
p-value*</td><td>1±10
ns</td><td>14±19
0.011</td><td>0.012</td></tr>
</table>
*p-value for comparison with pre-operative data.

Effect of body position on FVC
Body position had no effect on FVC in the ICNT group, but significantly affected it in the PNT group.
</td>
<td>including pulmonary function tests.
Other issues:
• Authors recommend that patients should rest in Fowler’s position postoperatively after PNT.
• Authors think that earlier muscle recovery in ICNT group might be because of the short distance of nerve growth needed.
• Authors recommend the use of ICNT rather than PNT and suggest PNT should be avoided in infants, children or patients with cardiopulmonary diseases.</td>
</tr>
</table>

Abbreviations used: ABPI, avulsed brachial plexus injuries; BPI, brachial plexus injury; CXR, chest fluoroscopy; DLCO, single breath diffusing capacity of the lung for carbon monoxide; FRC, functional residual capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; ICNT, intercostal nerve transfer; IC, inspiratory capacity; MCN, musculocutaneous nerve; MIT, multiple intercostal nerve transfer; MRC, medical research council; MVV, maximum ventilation volume; PFTs, pulmonary function tests; PNT, phrenic nerve transfer; RV, residual volume; SAN, spinal accessory nerve; SD, standard deviation; TV, tidal volume; TLC, total lung capacity; VC, vital capacity; Vo_2, oxygen uptake.

Study details

Dong Z (2010)[2]

Prospective case series

China

Recruitment period: 2002 to 2005

Study population: patients with ABPI (21 left and 19 right sided) from traffic accidents (34 cases), machine traction injury (3), fall from height (2) and explosion injury (1). Injury type: upper trunk injury (3 cases), upper and middle trunk injury (6), and total plexus injury (31 cases).

n=**40**

Age: mean 31 years

Sex: 87% (35/40) male

Patient selection criteria: not reported

Mean surgical delay: 4.6 months

Technique: The brachial plexus was explored and the upper trunk was found to be avulsed, preganglionic injury was confirmed by preoperative EMG. The phrenic nerve was identified on the surface of the anterior scalenus muscle and electrical stimulation elicited powerful contraction of the diaphragm, which was then divided distally. The upper trunk was dissected at the trunk divisional level, and the proximal end of the phrenic nerve was transferred to the anterior division of the upper trunk directly and attached using 8-0 nylon sutures. Other transfers were

Key efficacy findings

Number of patients analysed: **40**

Patient age and restoration of elbow function

Age (years)	**No of cases**	**Muscle strength MRC≥3**	**Muscle strength MRC<3**	**Effective rate (%)**
<40	32	29	3	90.6
≥40	8	4	4	50.0
Total	40	33	7	82.5

For most patients, weak biceps contraction could be seen 8–9 months after the surgery by initiating a breath, indicating the successful regeneration of the phrenic nerve into the biceps.

Surgical delay and effectiveness

Surgical delay (months)	**No of cases**	**Muscle strength MRC≥3**	**Muscle strength MRC<3**	**Effective rate (%)**
<6	32	29	3	90.6
6–12	4	3	1	75.0
>12	4	1	3	25.0
Total	40	33	7	82.5

Prolongation of latency and surgical effectiveness in the ipsilateral phrenic nerve

Prolongation of latency	**No of cases**	**Muscle strength MRC≥3**	**Muscle strength MRC<3**	**Effective rate (%)**
<10%	25	23	2	92.0
10–	9	7	2	77.8

Key safety findings

After transection of the phrenic nerve unilateral diaphragmatic paralysis was observed in all patients on plain chest radiographs, but no respiratory dysfunction was encountered because of the compensation of the intact diaphragm.

Comments

Study design issues:

- Single-centre study
- Direct neurotisation was performed.
- Motor evaluation was done using the British MRC grading system (ranging from grade 5 to grade 0, higher grades indicating better recovery).
- Preoperative electromyography on bilateral phrenic nerve recorded.

Other issues:

- The authors state that this procedure is simple and does not need

<table>
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<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>performed simultaneously where appropriate; for example as an accessory to suprascapular nerve transfer. The treated upper limb was immobilised for 4–6 weeks after surgery and electromyographic evaluation was done every 3 months to check the progress of nerve function.

Follow-up: average 28.2 months

Conflict of interest/source of funding: none.</td>
<td>
<table>
<tr><td>20%</td><td></td><td></td><td></td><td></td></tr>
<tr><td>>20%</td><td>6</td><td>3</td><td>3</td><td>50.0</td></tr>
<tr><td>Total</td><td>40</td><td>33</td><td>7</td><td>82.5</td></tr>
</table>

Attenuation of amplitude and surgical effectiveness in the ipsilateral phrenic nerve
<table>
<tr><th>Attenuation of amplitude</th><th>No of cases</th><th>Muscle strength MRC≥3</th><th>Muscle strength MRC<3</th><th>Effective rate (%)</th></tr>
<tr><td><10%</td><td>11</td><td>10</td><td>1</td><td>90.9</td></tr>
<tr><td>10–20%</td><td>10</td><td>8</td><td>2</td><td>80.0</td></tr>
<tr><td>>20%</td><td>19</td><td>15</td><td>4</td><td>78.9</td></tr>
<tr><td>Total</td><td>40</td><td>33</td><td>7</td><td>82.5</td></tr>
</table>

Regression analysis shows that the regression coefficients of surgical delay and prolongation of latency were negative, indicating that they are the factors related to the outcome of the surgery.
</td>
<td></td>
<td>a nerve graft. They recommend it in patients whose structures at the divisional level of the brachial plexus are intact.</td>
</tr>
</table>

<table>
<tr><td colspan="4">Abbreviations used: ABPI, avulsed brachial plexus injuries; BPI, brachial plexus injury; CXR, chest fluoroscopy; DLCO, single breath diffusing capacity of the lung for carbon monoxide; FRC, functional residual capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; ICNT, intercostal nerve transfer; IC, inspiratory capacity; MCN, musculocutaneous nerve; MIT, multiple intercostal nerve transfer; MRC, medical research council; MVV, maximum ventilation volume; PFTs, pulmonary function tests; PNT, phrenic nerve transfer; RV, residual volume; SAN, spinal accessory nerve; SD, standard deviation; TV, tidal volume; TLC, total lung capacity; VC, vital capacity; Vo_2, oxygen uptake.</td></tr>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Zheng MX (2012)[3]

Retrospective comparative study
China (single centre)
Recruitment period: 1990 to 2002
Study population: adult patients with unilateral ABPI
n=42 (PNT alone 19 vs. combined PNT+MIT 23)
Age: PNT: mean 28.73 years; PNT+MIT: mean 24.46 years
Sex: 83% (35/42) male

Patient selection criteria: healthy patients, with preoperative normal bilateral phrenic nerve functions (confirmed by phrenic nerve conduction study and chest fluoroscopy).
Exclusion criteria: external lung and/or heart diseases, history of thoracic trauma.

Technique: ABPI was confirmed by intraoperative electromyogram during surgical exploration. Ten surgeons performed the surgeries. When the BPI involved avulsion of only 1 to 3 roots (usually C5–C7 roots), PNT was performed and MIT was not. When more than 3 BP roots were avulsed (in complete ABPI), MIT was performed with PNT at the same stage or after 1 or 2 months. PFTs (FVC, FEV1, TLC and FRC in sitting position), phrenic nerve conduction (for response of PN</td>
<td>Number of patients analysed: 42 (PNT alone 19 vs. combined PNT+MIT 23)</td>
<td>Breathing difficulties
<table>
<tr><th>Dyspnoea</th><th>n</th></tr>
<tr><td>Breathing difficulties at rest or during mild activities</td><td>0</td></tr>
<tr><td>Exertional dyspnoea (could tolerate)</td><td>1 (heavy smoker/overweight patient in PNT)</td></tr>
<tr><td>Medium dyspnoea (at vigorous exercise: football, fast running)</td><td>7 (do activities for 15 minutes without break)</td></tr>
</table>
Pulmonary function (per cent of predicted values)
<table>
<tr><th>Variables</th><th>PNT (n=19)
mean ±SD</th><th>PNT+MIT (n=23)
mean ±SD</th><th>p value</th></tr>
<tr><td>FVC %</td><td>74.09±12.41</td><td>73.69±13.56</td><td>>0.05</td></tr>
<tr><td>FEV1 %</td><td>76.99±13.68</td><td>72.04±15.41</td><td>>0.05</td></tr>
<tr><td>TLC %</td><td>80.63±14.07</td><td>74.81±13.16</td><td>>0.05</td></tr>
<tr><td>FRC %</td><td>101.08±29.53</td><td>93.15±20.56</td><td>>0.05</td></tr>
<tr><td>FVC % supine</td><td>61.58±13.58</td><td>59.34±16.86</td><td>>0.05</td></tr>
<tr><td>FVC % reduction in supine</td><td>16.87±6.19</td><td>20.53±11.04</td><td>>0.05</td></tr>
</table>
Diaphragmatic excursion (n=42)
Before surgery, all patients had normal function of the ipsilateral diaphragm (confirmed on nerve conduction study and chest X-ray).</td>
<td>Study design issues:
All 42 patients had PNT, 19 had PNT alone, 23 had PNT combined with MIT (PNT+MIT group)
4 of the PNT+MIT patients underwent PNT and MIT procedures at the same stage, and 19 at an interval of 1–2 months.
Measurements were done by a technician who was blinded to procedures or type of nerves used.
FVC in sitting and supine positions were compared.
Pulmonary function results were normalised as</td>
</tr>
</table>

Abbreviations used: ABPI, avulsed brachial plexus injuries; BPI, brachial plexus injury; CXR, chest fluoroscopy; DLCO, single breath diffusing capacity of the lung for carbon monoxide; FRC, functional residual capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; ICNT, intercostal nerve transfer; IC, inspiratory capacity; MCN, musculocutaneous nerve; MIT, multiple intercostal nerve transfer; MRC, medical research council; MVV, maximum ventilation volume; PFTs, pulmonary function tests; PNT, phrenic nerve transfer; RV, residual volume; SAN, spinal accessory nerve; SD, standard deviation; TV, tidal volume; TLC, total lung capacity; VC, vital capacity; Vo_2, oxygen uptake.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
stimulation) and diaphragmatic excursion (chest fluoroscopy) were performed. Compound Muscle Action Potential of diaphragm muscle was also recorded. In the PNT+MIT group, further investigations were done on the effect of the number of transferred ICNs and the timing of MIT. Follow-up: **mean 10 years (range 7 to 19 years)** Conflict of interest/source of funding: grant by Chinese National Basic Research program; 'Dawn' Program of Shanghai Education Commission, China, and Program for New Century Excellent Talents in University, China.		A certain degree of hemidiaphragm elevation (a mean of 1–1.5 intercostal spaces) was observed in 90.48% (38/42) patients at mean 10 years. Diaphragmatic excursion was reduced by a mean of 0.5–1 intercostal space. Hemidiaphragm elevation and movement reduction did not increase as the number of ICNs grew from 2–4 in the PNT+MIT group or both procedures done at the same stage or performed at an interval of 1–2 months.	a percentage of reference values that were obtained from a healthy Chinese population. • 2 to 4 ICNs were used in most of the patients in the PNT+MIT group. **Study population issues**: • Demographic data for the 2 groups were comparable • Most patients had injury on the left side (26/42). **Other issues**: • Authors suggest MIT should be performed 1–2 months after PNT to avoid respiratory function impairment.

<table>
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<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>
Chuang ML (2005)[4]
Case series (single centre)
Taiwan
Recruitment period: 2000 to 2001
Study population: patients with ABPI and shoulder drop
n=19
Age: mean 25 years
Sex: 89% (17/19) male
Patient selection criteria: patients with limited range of motion of the injured arm and shoulder drop after BPI.
Time from injury to surgery: mean 3.7 months

Technique: PNT combined with MIT (PNT+MIT) (with or without SAN, ipsilateral C7, or cervical motor nerve roots) was performed in 15 patients. 2 had only PNT and 2 other patients had only MIT because of phrenic nerve paralysis after trauma in the lower cervical spine. 10 were done on the left and 9 on the right side. Postoperatively, after 3 weeks all patients took part in shoulder rehabilitation including physical therapy and electrical stimulation 3 days/week for 2 years. Ventilation was assessed before and after the surgery and every 6 months.
Follow-up: mean 21 months
Conflict of interest/source of funding: supported by Chang Gung Medical Research Committee.
</td>
<td>
Number of patients analysed: 19
Restoration of shoulder function
Shoulder abduction improved from a drop shoulder to a mean angle of 95±49°.
</td>
<td>
Ventilation and exercise performance
<table>
<tr><th></th><th>Before operation % (n)</th><th>After operation % (n)</th></tr>
<tr><td>Dyspnoea on exertion*</td><td>21% (4/19)</td><td>42% (8/19) mild dyspnoea within 6 months (p<0.05), resolving by 1 year</td></tr>
<tr><td>Diaphragm excursion** (on chest ultrasonography)</td><td>10.5% (2/19) (limited because of lower spine injury)</td><td>100% had ipsilateral diaphragm paralysis for up to 36 months compared with pre-operative state(p<0.01)</td></tr>
<tr><td>PFT</td><td>37% (7/19) (normal)</td><td>8% decrease in FVC, TLC, IC (all p<0.05) within 6 months that persisted for 3 years.</td></tr>
<tr><td></td><td>DLCO decreased after trauma</td><td>11% increase (p<0.01) between 6 months and 3 years***</td></tr>
<tr><td>Cardiopulmonary exercise performance (CPET)</td><td>Peak Vo2 and minute ventilation (Ve) were 1.59±0.36 and 62±16 L/min</td><td>Cardiovascular function improved in the first 6 months and continued improving for up to 3 years. Ventilation increased 6% per 6 months, overall 8% improvement in peak Vo2 (r=0.54; p<0.001)</td></tr>
</table>
*graded on a scale nil to severe.
**graded on a scale 0–3 (0 for no movement, 0.5 for movement <1 intercostal space [ICS], 1 for 1 ICS, 1.5 for >1 and <2 ICSs, 2 for 2 ICSs, 3 for >2 ICSs).
*** Because of an improvement in exercise performance and ventilation efficiency after surgery.
</td>
<td>
Study design issues:
9 patients enrolled within 1 week and 10 enrolled after the procedure because they had no medical conditions and normal lung function and exercise capacity could be normalised as % of normal predicted values.
Study population issues:
ABPI was because of a motorcycle accident in 17 and a chemical explosion in 2 patients.
Despite injury all patients were able to perform their daily activities.
</td>
</tr>
</table>

<table>
<tr><td colspan="4">Abbreviations used: ABPI, avulsed brachial plexus injuries; BPI, brachial plexus injury; CXR, chest fluoroscopy; DLCO, single breath diffusing capacity of the lung for carbon monoxide; FRC, functional residual capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; ICNT, intercostal nerve transfer; IC, inspiratory capacity; MCN, musculocutaneous nerve; MIT, multiple intercostal nerve transfer; MRC, medical research council; MVV, maximum ventilation volume; PFTs, pulmonary function tests; PNT, phrenic nerve transfer; RV, residual volume; SAN, spinal accessory nerve; SD, standard deviation; TV, tidal volume; TLC, total lung capacity; VC, vital capacity; Vo_2, oxygen uptake.</td></tr>
<tr><td>Study details</td><td>Key efficacy findings</td><td>Key safety findings</td><td>Comments</td></tr>
<tr><td>Gu YD and Ma M (1996)[5]
Retrospective case series
China
Recruitment period: 1970 to 1990
Study population: patients with BPI
n=180
Age: average 23.6 years
Sex: 85% (153/180) male
Mechanism of injury: traffic accidents (46%), occupational accidents (37%), obstetric damage (2%), sports injuries (6%) or penetrating wounds (4%).
Left side injury (60%), right side injury (38%), both sides (2%).
Level of injury: total brachial avulsion (n=120), lower trunk spared (n=60).
Time from injury to surgery: mean 327 days
Patient selection criteria: not reported.
Technique: phrenic nerve function confirmed on EMG and sectioned. Proximal end coapted to distal segment of the MCN, directly or via nerve graft, sometimes using magnification. Nerve graft used when tension observed on direct coaptation. Postoperatively, a head thoraco-shoulder spica applied for 4–6 weeks followed by neck motion and shoulder training, EMG evaluation done every 3 months.
Follow-up: average 4.5 years (range 2–13.6 years)
Conflict of interest/source of funding: not reported.</td>
<td>Number of patients analysed: 65
Biceps functional recovery (n=65)
<table>
<tr><th>Type of neurotisation</th><th>Total</th><th>M-5</th><th>M-4</th><th>M-3</th><th>M-2/0</th></tr>
<tr><td>Phrenic -graft MCN</td><td>9</td><td>0</td><td>5</td><td>4</td><td>0</td></tr>
<tr><td>Phrenic-MCN</td><td>40</td><td>3</td><td>16</td><td>13</td><td>8</td></tr>
<tr><td>Phrenic-others</td><td>16</td><td>2</td><td>8</td><td>4</td><td>2</td></tr>
<tr><td>Total</td><td>65</td><td>5</td><td>29</td><td>21</td><td>10</td></tr>
</table>
84.6% (55/65) regained biceps power to M3 or greater strength.

Factors influencing outcomes
The average time taken for muscular strength restoration of biceps to grade M3 was 9.5 months (range 3–30 months).
The average duration of treatment delay for the M4 to M5, the M3, and the M2 to M0 recovery groups were 291.2, 421.2 and 656.4 days, respectively. The longer the delay in treatment, the worse the outcome.
Patients who received an innervating nerve graft to achieve a tension-free coaptation had results as good as other patients with direct coaptation procedures.
91% (20/22) of children regained biceps power to M3 or greater strength. Only 2 of the 3 patients older than 50 years had effective results.
Poor results were seen with severe crushes and associated fractures in the shoulder region.</td>
<td>Pulmonary function (n=65)
Transient dyspnoea occurred in 1 patient (5-year-old child who had PNT and ipsilateral 4, 5 and 6 ICN transfer at the same time).
Diaphragmatic elevation (on chest fluoroscopic examination) (n=40)
1 year after surgery, 80% (32/40) patients had diaphragmatic elevation.
5 years after surgery, 12% (5/40) patients had persistent limitations of diaphragmatic excursions. None of them had associated respiratory insufficiency.
Pulmonary function tests (n=19)
Results on lung function (including FVC, TLC, FRC, VC and MVV) showed decreased pulmonary capacities in all patients within 1 year of surgery, recovered to normal values by 2 years.</td>
<td>Follow-up issues:
• Patients with follow-up of >2 years were included.
Study design
• Motor evaluation done using British MRC grading system (ranging from grade 5 to grade 0, higher grades indicating better recovery).
• Time taken for the return of a biceps muscle power rating of M3 was used as an indicator of return of motor function.</td></tr>
</table>

Abbreviations used: ABPI, avulsed brachial plexus injuries; BPI, brachial plexus injury; CXR, chest fluoroscopy; DLCO, single breath diffusing capacity of the lung for carbon monoxide; FRC, functional residual capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; ICNT, intercostal nerve transfer; IC, inspiratory capacity; MCN, musculocutaneous nerve; MIT, multiple intercostal nerve transfer; MRC, medical research council; MVV, maximum ventilation volume; PFTs, pulmonary function tests; PNT, phrenic nerve transfer; RV, residual volume; SAN, spinal accessory nerve; SD, standard deviation; TV, tidal volume; TLC, total lung capacity; VC, vital capacity; Vo_2, oxygen uptake.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Luedemann W (2002)[6] **Retrospective case series** Germany (single centre) Recruitment period: 1980 to 1999 Study population: patients with complete BPI and root avulsions n=**23** Age: mean 25 years Sex: not reported Patient selection criteria: patients with clinical, electrophysiological and radiological evidence of complete BP palsy and root avulsions. Root avulsion determined by MRI, myelography and postmyelographic CT of the cervical spine, in some cases, dorsal inspection by hemilaminectomy. Technique: PNT to the MCN was performed with a combined supra and infraclavicular approach, with direct connection in 5 patients. A sural autograft (mean length 11 cm) was needed in 18 patients. All had neurotisation with ipsilateral phrenic nerve. Preoperative and postoperative pulmonary functional parameters were compared and body plethysmography was performed 12 months after surgery. Follow-up: **range 12 to 42 months** Conflict of interest/source of funding: not reported.	Number of patients analysed: **12** (5 left sided and 7 right sided PNT) **Biceps muscle strength** Biceps muscle strength reached grade 4 in 58% (7/12) of the patients and only 1 patient had disappointing functional result (grade 0). The 7 patients excluded from analysis had biceps muscle strength grade 3–4. No correlation between the length of the transplanted nerve and final muscle strength was observed.	No patients experienced breathing problems. 1 patient with right-sided PNT showed significant hemidiaphragmatic palsy (on chest X-ray). **Pulmonary function** In right-sided PNT, VC reduction was significant, at 14.3±3.3% (mean±SD) (p=0.0003) whereas left-sided PNT showed a non-significant reduction of 3.6±3.5% (mean±SD). No difference was found between right- and left-sided FEV in VC% (with a mean reduction of 7%), % of predicted TLC values (86% on right side, 91.8% on left side), and % of predicted FRC values (104% on right side and 112% on left side).	**Follow-up issues:** • 4 patients lost to follow-up and 7 excluded from analysis due to severe lung contusions as part of injury. **Study design issues:** • VC%, FRC and TLC compared with predicted values by the European Respiratory Society's guidelines. • 10 patients were regular smokers. **Other issues:** • Authors recommend pulmonary examination, (PI_{max}) before PNT to avoid decrease in pulmonary function.

<table>
<tr><td colspan="4">Abbreviations used: ABPI, avulsed brachial plexus injuries; BPI, brachial plexus injury; CXR, chest fluoroscopy; DLCO, single breath diffusing capacity of the lung for carbon monoxide; FRC, functional residual capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; ICNT, intercostal nerve transfer; IC, inspiratory capacity; MCN, musculocutaneous nerve; MIT, multiple intercostal nerve transfer; MRC, medical research council; MVV, maximum ventilation volume; PFTs, pulmonary function tests; PNT, phrenic nerve transfer; RV, residual volume; SAN, spinal accessory nerve; SD, standard deviation; TV, tidal volume; TLC, total lung capacity; VC, vital capacity; Vo_2, oxygen uptake.</td></tr>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>
Xu W-D (2005[7], 2001[8])
Retrospective case series
China (single centre)
Recruitment period: 1999 to 2001
Study population: patients with total ABPI
n= 15 full length PNT vs 29 traditional PNT
Age: average age 27.4 years
Sex: 87% (13/15) male
Time from injury to surgery: mean 155 days
Patient selection criteria: not reported.
Technique: double cavity general anaesthesia was given. Video assisted thoracic surgery (with a Stryker 10mm thoracoscope) done to harvest a full-length phrenic nerve (severed at its entry into the diaphragm muscle) and transferred to MCN by interrupted 8-0 nylon sutures through the epineurium of the 2 nerves. The accessory phrenic nerve was not spared. Additional length was mean 12.3 cm.
7 were performed on the left and 8 on the right side. Thoracic drainage tubes were placed for 2–3 days and patients discharged within 1 week. At the second week, regular rehabilitation exercises with 500–1000 elbow flexion’s daily during deep breathing were given. Follow-up examinations done every 3 months in first year and every year thereafter.
Follow-up: 42 to 48 months
Conflict of interest/source of funding: not reported.
</td>
<td>
Number of patients analysed: 15 vs 29

Biceps functional muscle recovery
<table>
<tr><th></th><th>% (n) with new-born potential in the biceps</th><th>% (n) of patients achieving grade M3 recovery</th></tr>
<tr><td>Full-length PNT*</td><td>90%
(n=10/11),
after a mean of 140.5±34.7 days</td><td>72.7%
(n=8/11),
after a mean of 198.8±36.0 days</td></tr>
<tr><td>Traditional PNT</td><td>82.7,
(n=24/29),
after a mean of 247.1±90.3 days</td><td>79.3%
(n=23/29),
after a mean of 378.2±103.4 days</td></tr>
<tr><td>t-test</td><td>t=4.971
p<0.001</td><td>t=5.996
p<0.01</td></tr>
</table>
*27% (3/11) patients achieved M0–M2 recovery after 27 months’ follow-up.
</td>
<td>
No surgical complications reported.
No patients had breathing problems and none had breathing restrictions during physical activities.
Diaphragmatic elevation (n=15)
After 4 years’ follow-up, all patients sustained varying degrees of diaphragmatic paralysis and elevation (1–1.5 intercostal spaces) on the surgically treated side (seen on chest X-rays).
Change in pulmonary function (pre and postoperative)
<table>
<tr><th>Variable</th><th>Preop</th><th>6 months</th><th>1 year</th><th>3 years</th><th>Recent (not defined)</th></tr>
<tr><td>VC</td><td>3.71</td><td>3.63</td><td>3.85</td><td>3.79</td><td>3.80</td></tr>
<tr><td>RV</td><td>2.12</td><td>2.15</td><td>2.17</td><td>2.12</td><td>2.09</td></tr>
<tr><td>TLC</td><td>5.84</td><td>5.68</td><td>5.74</td><td>5.87</td><td>5.89</td></tr>
<tr><td>FVC</td><td>3.71</td><td>3.73</td><td>3.76</td><td>3.80</td><td>3.79</td></tr>
<tr><td>FEV1</td><td>3.36</td><td>3.03</td><td>3.32</td><td>3.36</td><td>3.34</td></tr>
</table>
Values are presented in litres of oxygen

PFTs (including VC, RV TLC, FVC and FEV1) recovered to preoperative levels by 1 year after surgery. The change in values before and after surgery was not statistically significant except for FEV1 values, which had a statistically significant reduction (t=1.395, t<t 0.05 (10) and p>0.05).
The postoperative maximal inspiratory pressure (PImax) value was significantly decreased compared with predicted values (average decrease 20%) in all patients at 4 years after surgery.
</td>
<td>
Follow-up issues:
4 patients lost to follow-up
Study design issues:

Preoperative PFTs, EMG demonstrated normal PFTs and bilateral phrenic nerve function.
Similar baseline characteristics between groups.
Patients with thoracic trauma excluded.
86.7% patients had injury due to motor accidents.
Authors suggest unilateral diaphragmatic paralysis could reduce the inspiration muscle force.

</td>
</tr>
</table>

Efficacy

A quasi-randomised study comparing phrenic nerve transfer (PNT; n=17) against intercostal nerve transfer (n=19) to the musculocutaneous nerve in 36 patients reported that motor recovery of biceps occurred significantly later in the PNT group (mean 262 days) than in the intercostal nerve transfer group (mean 195 days; p=0.03). Biceps muscle motor recovery to Medical Research Council (MRC) grade 3 (able to overcome gravity) or greater strength was reported in 29% (5/17) of patients in the PNT group and 53% (10/19) of patients in the intercostal nerve transfer group at 1-year follow-up. In the PNT group 23% (4/17) of patients had no recovery, but all patients in the intercostal nerve transfer group regained some muscle motor function, and after rehabilitation could separate breathing from biceps function[1].

A case series of 40 patients treated by PNT to the anterior division of the upper trunk of the brachial plexus to restore elbow flexion reported that the biceps muscle strength recovered to MRC grade 3 or greater in 83% (33/40) of patients and grade 0–2 (unable to overcome gravity) in 17% (7/40) of patients at an average follow-up of 28.2 months. Recovery to MRC grade 3 or greater strength occurred in 91% (29/32) of patients aged under 40 years, and in 50% (4/8) of patients aged 40 years and over. For patients who had the procedure more than 1 year after the injury, the recovery rate was 25% (1/4 patients)[2].

A retrospective case series of 180 patients treated by PNT to the musculocutaneous nerve (MCN) followed up 65 patients for more than 2 years. The study reported that 85% (55/65) of patients regained biceps muscle power to MRC grade 3 or greater strength. The average time taken for restoration of muscle strength to MRC grade 3 was 9.5 months. Longer delays in treatment were associated with lower levels of recovery. Patients who had a nerve graft had similar results to patients who had a direct nerve transfer. Poor results were seen in patients with severe crush injuries and associated fractures in the shoulder region[5].

A retrospective case series, comparing full-length PNT (n=15) and traditional PNT (n=29) to MCN reported that the mean time to grade 3 recovery was much earlier in the full-length PNT group than in the traditional PNT group (198 days compared with 140 days, p<0.01)[8].

Safety

Diaphragmatic elevation or paralysis

A retrospective comparative study of 42 patients comparing PNT (n=19) against PNT with multiple intercostal nerve transfer (PNT+MIT; n=23) reported that a certain degree of hemidiaphragm elevation (a mean of 1–1.5 intercostal spaces) was observed in 90% (38/42) of patients at a mean follow-up of 10 years. Diaphragmatic excursion was reduced by a mean of 0.5–1 intercostal spaces in both the groups after the procedures. Hemidiaphragm elevation and movement reduction did not worsen as the number of intercostal nerves used increased from 2–4 in the PNT+MIT group, or if both procedures were done at the same stage or performed at an interval of 1–2 months[3].

The case series of 19 patients treated by PNT+MIT reported persistent ipsilateral diaphragmatic paralysis in all patients for up to 36 months compared with the preoperative state ($p<0.01$)[4].

The retrospective case series of 65 patients reported that 80% (32/40) of patients had diaphragmatic elevation at 1-year follow-up. At 5-year follow-up, 12% (5/40) of patients had persistent limitations of diaphragmatic excursions. None of them had associated respiratory insufficiency[5].

The retrospective case series of 15 patients treated by full-length PNT reported that all patients sustained varying degrees of diaphragmatic paralysis and elevation (1–1.5 intercostal spaces) on the treated side after 4-year follow-up[7].

A retrospective case series of 23 patients reported that 1 patient treated by right-sided PNT showed significant hemidiaphragmatic palsy (on chest X-ray)[6].

Changes in pulmonary function

The quasi-randomised study of 36 patients comparing PNT (n=17) against intercostal nerve transfer (ICNT; n=19) reported that pulmonary function (forced vital capacity [FVC], forced expiratory volume in 1 second [FEV1], vital capacity [VC] and tidal volume [TV]) was significantly lower in the PNT group than in the ICNT group throughout 1 year of follow-up. Body position had a significant effect on forced vital capacity in the PNT group but no effect in the ICNT group[1].

The retrospective comparative study of 42 patients reported that FVC, FEV1 and total lung capacity (TLC) were 74%, 72% and 75% of predicted values in the PNT+MIT group, with no statistically significant differences from the PNT group. In the combined PNT+MIT group no further decrease in pulmonary function test results occurred when transferring 3 or 4 ICNs instead of transferring 2 ICNs. There were no significant differences within the PNT+MIT group whether or not PNT and MIT were performed at the same time or with an interval of 1–2 months[3].

The case series of 19 patients treated by PNT+MIT reported an 8% decrease in inspiratory capacity, FVC and TLC. There was an 11% increase in diffusing capacity between 6-month and 3-year follow-up[4].

The retrospective case series of 65 patients reported that pulmonary function tests in 19 patients (including forced vital capacity, total lung capacity, functional residual capacity, vital capacity and maximum ventilation volume) showed decreased pulmonary function during the first year after PNT surgery, improving to normal values by 2 years[5].

The retrospective case series of 23 patients reported that pulmonary function tests in patients who had PNT on the right side (n=7) showed a significant reduction in vital capacity of 14.3±3.3% (mean± standard deviation) (p=0.0003), whereas left-sided PNT (n=5) showed a non-significant reduction of 3.6±3.5% (mean± standard deviation). No difference was found between right- and left-sided FEV1 in VC% (with a mean reduction of 7% with either sided PNT). TLC values were reduced to 86% of predicted after right sided PNT, 91.8% on left sided PNT. Post-operative functional residual capacity (FRC) values were 104% after right sided PNT and 112% on the left[6].

The retrospective case series of 15 patients after full-length PNT reported that pulmonary function test results recovered to preoperative levels at 1-year follow-up. The postoperative maximal inspiratory pressure (PI_{max}) value was significantly decreased compared with predicted values (average decrease 20%) in all patients at 4-year follow-up[7].

Dyspnoea

The case series of 19 patients after PNT+MIT reported mild dyspnoea on exertion in 42% (8/19) of patients at 6-month follow-up (p<0.05), which resolved by 1-year follow-up[4].

The retrospective comparative study of 42 patients comparing PNT (n=19) and PNT+MIT (n=23) reported exertional dyspnoea in 1 patient (reported as being a heavy smoker and overweight) in the PNT group and medium dyspnoea on vigorous activity in 7 patients (treatment group not specified, both groups underwent PNT)[3].

The retrospective case series of 65 patients reported transient dyspnoea in 1 patient (5-year-old child) who had concomitant PNT and ipsilateral 4,5 and 6 ICN transfer[5].

Validity and generalisability of the studies

- Most of the studies retrospectively analysed long-term respiratory function in PNT or PNT+MIT.
- Very few prospective studies included both preoperative and postoperative measures of functional recovery and pulmonary function.
- Most studies were from China and East Asia, only 1 study was from Europe (Germany).
- Most of the patients were younger patients, with a mean age range between 23 and 31 years. Most of them were men, with total brachial avulsion or trunk

injuries caused by accidents. There were very few patients with obstetric damage.

- The follow-up period ranged from mean 12 months to 10 years.
- Most of the patients had the operation less than 6 months after injury.
- Different surgical methods were reported (traditional PNT, full-length PNT, PNT in combination with multiple intercostal nerve transfer). One study compared PNT with MIT and another study compared PNT with full-length PNT.
- Large retrospective case series with long-term follow-up reported good motor function without any effect on pulmonary parameters.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

There is currently no NICE guidance related to this procedure.

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their specialist society or royal college. The advice received is their individual opinion and does not represent the view of the society.

Christopher Duff, Mr Henk Giele and Mr Andrew Hart (British Association of Plastic and Reconstructive and Aesthetic Surgeons).

- Two specialist advisers have never performed this procedure and 1 adviser has performed it at least once. One of these advisers stated that this is a specialised area of surgery performed by few plastic, orthopaedic and neurosurgeons. One adviser stated that the procedure is contraindicated for obstetric brachial plexus injuries.
- 1 specialist adviser proposed an alternative title: partial/complete ipsilateral phrenic nerve transfer in adult brachial plexus injury reconstruction.

- 1 specialist adviser considered it as an established practice and no longer new, whereas another adviser stated that it is not an established practice in the UK. Another adviser stated that it is definitely a novel procedure and of uncertain safety and efficacy.
- Comparators for this procedure include reconstruction with nerve grafts, intraplexal/other extraplexal nerve transfers/neurotisation using other nerves such as accessory nerve, intercostal nerves, and fascicles of the ulnar nerve, radial nerve and/or median nerve.
- Three specialist advisers stated that less than 10% of specialists are engaged in this area of work.
- Theoretical adverse events include loss of ipsilateral diaphragmatic control resulting in impaired ventilator capacity, respiratory distress, loss of vital capacity, loss of exercise tolerance, chest wall deformity, raised diaphragm, herniation, basal atelectasis/collapse, chest infection, need for prolonged mechanical ventilation, poor voluntary control of muscles innervated by the transfer and failure to re-innervate target muscles due to proximal injury to the phrenic nerve.
- Key efficacy outcomes include recovery/restoration of muscle function or joint movement/elbow flexion (that is, MRC grade 3/5 or more muscle function is classified as a good response), shoulder stability, control of re-innervated muscle, voluntary contraction and functional scores such as DASH (Disabilities of the Arm, Shoulder and Hand) and QALY (quality-adjusted life year) measures.
- There are uncertainties about the efficacy of the procedure and the associated donor site morbidity as a major nerve is sacrificed. One adviser stated that from a functional perspective, grade 3 equates only to an ability to flex the joint against gravity. This fails to account for the ability of the muscle for sustained contraction, both of which are essential for function. The majority (>80%) of the reported results are in grade 3 category and based on the ability to perform joint movement rather than a functional score. He also stated that the

muscle involuntarily contracts and the neurological control of the repair is uncertain.

- One adviser stated that the procedure is driven by enthusiasts rather than objective assessment. He stated that all published work is confounded by small sample sizes, selection criteria, heterogeneity of patients, comorbidity, age, management of the rest of the plexus injury, intercostal nerve functional status, and issues pertaining to the adequacy of outcome measures. There are no long-term data on respiratory function as chronic disease and age-related deterioration occurs.
- Extensive clinical and surgical training in microsurgery, peripheral nerve reconstruction, nerve grafting and brachial plexus reconstruction is needed. It should be undertaken in units with facilities for brachial plexus repair.
- One specialist adviser stated that the speed of diffusion is slow, whereas 2 advisers stated that it is an old established procedure and already maximally diffused.
- Three specialist advisers stated that fewer than 10 specialist centres in the UK are likely to carry out this procedure and the impact on the NHS, in terms of number of patients and use of resources, will be minor as these types of injuries needing reconstruction are relatively infrequent. This procedure has not been widely adopted due to the lack of efficacy in terms of function and control of muscle and donor site morbidity.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

- There is no evidence on efficacy outcomes such as pain relief, time to recovery or quality of life.

- Evidence shows that the diaphragm on the operated side is paralysed or elevated as a result of dividing the phrenic nerve causing respiratory problems.

References

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2. Zheng MX, Qiu YQ, Xu WD et al. (2012) Long-term observation of respiratory function after unilateral phrenic nerve and multiple intercostal nerve transfer for avulsed brachial plexus injury. Neurosurgery 70 (4): 796–801.

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4. Chuang M-L, Chuang DCC, Lin I-F et al. (2005) Ventilation and exercise performance after phrenic nerve and multiple intercostal nerve transfers for avulsed brachial plexus injury. Chest.128 (5): 3434–9.

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6. Luedemann W, Hamm M, Blomer U et al. (2002) Brachial plexus neurotization with donor phrenic nerves and its effect on pulmonary function. Journal of Neurosurgery 96 (3): 523–6.

7. Xu WD, Gu YD, Lu JB et al. (2005) Pulmonary function after complete unilateral phrenic nerve transection. Journal of Neurosurgery 103 (3): 464–7.

8. Xu WD, Gu YD et al. (2002) Full-length phrenic nerve transfer by means of Video-Assisted Thoracic Surgery in treating brachial plexus avulsion injury. Plastic and reconstructive surgery 110 (1): 104–9

Appendix A: Additional papers on phrenic nerve transfer in brachial plexus injury

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Chuang DC, Epstein MD, Yeh MC (1993) (1993) Functional restoration of elbow flexion in brachial plexus injuries: results in 167 patients (excluding obstetric brachial plexus injury). Journal of Hand Surgery - American Volume 18 (2): 285–91.	Case series n=167 (only 1 PNT) Patients with BPI Intervention: surgical procedures (nerve reconstruction =128 and muscle tendon transfer=39). Follow-up: 2 years	Nerve reconstruction was superior to muscle tendon transfer. Direct suturing was superior to nerve grafting. Short nerve grafts were superior to long nerve grafts, infraclavicular injuries did better than supraclavicular injuries, vascularised ulnar nerve grafts were superior to conventional long nerve grafts, ruptured plexus injuries recovered better than root avulsions, ICN transfer to the MCN has satisfactory results. Results of PNT to MCN in 1 patient were fair.	Nerve reconstruction included direct suturing, nerve grafting, or nerve transfer to MCN (donor nerves are PN, ICN, SAN) only 1 patient had PNT
Chuang D C, Lee GW, Hashem F (1995) Restoration of shoulder abduction by nerve transfer in avulsed brachial plexus injury: evaluation of 99 patients with various nerve transfers. Plastic & Reconstructive Surgery 96 (1): 122–8.	Case series n=99 Patients with total or upper root avulsions BPI Intervention: various nerve transfers (8 different combinations of coaptations between various donor nerves) PNT used to neurotise SSN and AXN with a nerve graft (n=37) Follow-up: 2 years	Simultaneous neurotisation of the SSN and AXN with PN and SAN obtained better shoulder abduction. Neurotisation of C5 spinal nerve by multiple nerve transfers was another good option that yielded good shoulder abduction in 1 patient.	8 different combinations of coaptations between various donor nerves. Different results for each category.
El-Gammal T A and Fathi NA (2002) Outcomes of surgical treatment of brachial plexus injuries using nerve grafting and nerve transfers. Journal of Reconstructive Microsurgery 18 (1): 7–15.	Case series n=32 (18 PN neurotisation) Indication: BPI Different techniques of nerve reconstruction (Nerve grafting (18) and nerve transfers (71)) Follow-up: average 35 months	Biceps motor recovery function was best following grafting the MCN or neurotisation with PN n=3 (100% grade 4) followed by neurotisation with ICN (89.5%, grade 3) and grafting the C5 root or upper trunk (grade 3). PN to SSN (n=3) produced the best results of shoulder abduction (40 to 90 degrees), followed by combined neurotisation of SAN to SSN and PN to AXN (n=8) (20 to 90 degrees). Sensory recovery over the lateral forearm and palm varied from S2 to S3.	Multiple techniques of nerve reconstruction used and for nerve transfers many donor nerves used.
El-Gammal, T A, El-Sayed A, and Kotb MM	Case series	Elbow flexion was restored in all but 2	Different neurotisation procedures for elbow

(2003) Surgical treatment of brachial plexus traction injuries in children, excluding obstetric palsy. Microsurgery 23 (1): 14–7.	n=11 BPI in children who had car accidents 6 intrafascicular grafting and 25 extraplexal neurotizations done. Donor nerves included ICN, PN, SAN and contralateral C7 root. Follow-up: 30 months	cases. Shoulder abduction varied from 30-90 degrees according to the method of reconstruction. Triceps recovered in 2 cases, and finger and wrist extensors in 1 case.. Sensory recovery in the palm reached S2/S2+. Harvesting the phrenic nerve and contralateral C7 root resulted in no residual mortality.	and shoulder reconstruction used. Neurotisation of the axillary and suprascapular nerves, MCN, SAN with phrenic nerve was done in 6 cases.
Flores LP (2011). Triceps brachii reinnervation in primary reconstruction of the adult brachial plexus: experience in 25 cases. Acta Neurochirurgica 153 (10): 1999–2007.	Retrospective analysis n=25 Adults with BPI Intervention: reinnervation of triceps or radial nerve (various techniques used including posterior cord reconstruction and nerve transfers) various donor nerves used (C7 root, PN, MPN, ICN, SAN, UN) Only 7 patients had PNT.	21/25 (83%) patients obtained triceps reinnervation, good results were seen in 76% (19/25) cases. M4 grade in 36%, M3 in 40%, M2 in 8%, M1 in 8% and M0 in 8% cases. Best outcomes were seen in C5 to C7 palsy and in those in which the triceps was chosen as the target.	Heterogeneous group of patients with BPI in whom a number of different techniques for reinnervation was used. Multiple nerve transfers were performed of these only 7 had PNT to radial nerve.
Flores LP (2011) Brachial plexus surgery: the role of the surgical technique for improvement of the functional outcome. Arquivos de Neuro-Psiquiatria 69 (4): 660–5.	Retrospective analysis n=99 Patients with traumatic BPI Intervention: Different nerve transfers done, different surgical techniques used (PNT-MCN=28 cases). Follow-up: mean 32.5 months	Proximal nerve root grafting was associated with good results in 70% cases. Significantly better outcomes seen in Oberlin’s procedure and the Sansak procedure. Improvement in outcomes associated with PN, MCN and the accessory or SSN transfer did not reach statistical significance. Reinnervation of the hand was seen in less than 30% cases.	Different nerve transfers done and different surgical techniques used.
Gu YD, Wu, MM et al (1989). Phrenic nerve transfer for brachial plexus motor neurotization. Microsurgery 10 (4) 287-9.	Retrospective case series n=164 Patients: with brachial plexus root avulsion injuries Intervention: mainly PNT to MCN (and a variety of other recipient nerves) Follow-up: average 4.5 years	65 patients presented a follow-up of more than 2 years. 84.6% (55/65) achieved a recovery of M3 or better. Only 1 patient demonstrated clinically significant respiratory problem which was resolved with treatment. No long term deleterious effects on respiratory function were observed.	Multiple publication Similar study included in table 2.
Gu YD, Wu, MM et al	Retrospective case	65 patients presented a	Multiple publication

(1990). Phrenic nerve transfer for treatment of root avulsion of the brachial plexus.Chinese Medical Journal 103 (4) 267-70.	series n=164 Patients: with brachial plexus root avulsion injuries Intervention: mainly PNT to MCN (and a variety of other recipient nerves) Follow-up: average 4.5 years	follow-up of more than 2 years. 84.6% (55/65) achieved a recovery of M3 or better. Only 1 patient demonstrated clinically significant respiratory problem which was resolved with treatment. No long term deleterious effects on respiratory function were observed. The surgical effects are related to severity of injury, duration, mode of operation and patient's age.	Similar study included in table 2.
Gu YD, Zhang GM and Wu MM (1987). Microsurgical treatment for root avulsion of the brachial plexus. Chinese Medical Journal.100 (7): 519-22.	Retrospective case series n=108 Patients: with brachial plexus root avulsion injuries Intervention: PNT, accessory nerve, motor branches of the cervical plexus and ICN Follow-up: average 6.8 years		Multiple publication Similar study included in table 2.
Hou, Z and Xu, Z (2002). Nerve transfer for treatment of brachial plexus injury: comparison study between the transfer of partial median and ulnar nerves and that of phrenic and spinal accessary nerves. Chinese Journal of Traumatology 5 (5) 263-6.	Comparative study n=23 Intervention: nerve transfer for BPI (Group 1- PN and SAN transfer [n=12] vs Group 2-median and ulnar nerves transfer [n=11]) Follow-up: average 2.25 years	16.6% (2/12) patients in group 1 had the recovery of M4 strength of biceps muscle, compared to 63.6% (7/11) in group 2, and the difference was statistically significant ($p<0.025$). All nerve transfers were effective for restoration of elbow or shoulder function, but the nerve transfer using median and ulnar nerves obtained more powerful biceps muscle strength than PN and SAN transfer.	PNT to MCN and SAN to SSN was done in combination and compared to partial median and ulnar nerve transfer.
Lin H, Hou C, Chen A et al. (2011) Transfer of the phrenic nerve to the posterior division of the lower trunk to recover thumb and finger extension in brachial plexus palsy. Journal of Neurosurgery 114 (1): 212–6.	Case series n=10 (mean age 27.2 years) Patients with BP palsy Intervention: PNT to the posterior division of the lower trunk. Mean interval from injury to surgery 5.7 months Follow-up: average 3.5	8 patients recovered to MRC grade 3 or better in extensor digitorium strength and 7 patients recovered to grade 3 or better in extensor policis strength. No major complications related to surgical procedure. None showed any clinical signs or	Larger studies included in table 2.

	years	symptoms of respiratory insufficiency.	
Lin H, Hou C, and Chen D (2012) Full-length phrenic nerve transfer as the treatment for brachial plexus avulsion injury to restore wrist and finger extension. Muscle & Nerve 45 (1): 39–42.	prospective study n=6 (mean age 28 .7 years) Patients with complete BP avulsion injury Intervention: full length PNT to medial part of radial nerve via endoscopic thoracic surgery Follow-up: average 3.3 years	In 5 patients, extensor capri ulnaris and extensor capri radialis strength recovered to MRC grade >M3 and in 4 patients extensor digitorium strength recovered to M3. No major complications related to surgical procedure. None showed any clinical signs or symptoms of respiratory insufficiency	Larger studies included in table 2.
Monreal, R. (2007). Restoration of elbow flexion by transfer of the phrenic nerve to musculocutaneous nerve after brachial plexus injuries. Hand 2 (4) 206-11.	Case series (prospective study) n=25 Patients: Adults with BP traction/crush lesion (complete BPI=12, C5-6 injury =8) Intervention: PNT to MCN as no evidence of muscle function 3 months post injury. Follow-up: mean 31.3 months	Functional elbow flexion was obtained in majority of the cases by phrenic-musculocutanoeus nerve transfer (14/20, 70%) Reinnervation of biceps muscle noted at a mean 7.2 months. At final follow-up, elbow flexion strength was a MRC grade 5 in 2 patients, grade 4 in 4 patients, grade 3 in 8 patients, grade 2 or less in 6 patients. The longer the operative delay the poorer the result. No significant relationship between surgical outcomes, patient age and length of implant.	Study assessed only restoration of elbow function. Other studies that also assessed pulmonary function parameters were included in table 2.
Nagano A, Yamamoto S, and Mikami Y (1995) Intercostal nerve transfer to restore upper extremity functions after brachial plexus injury. Annals of the Academy of Medicine, Singapore 24 (4:Suppl) Suppl-5.	Case series n=112 (PNT to SSN=7) Patients with BPI Intervention: combined operation of ICN to MCN and ICN to AXN and PNT to SSN. Follow-up: mean 27 months (PNT); mean 40 months (ICN)	97 (87%) of them regained grade 3/4 elbow flexion. Of 7 who had nerve transfer for loss of shoulder function, 4 regained > 80 degrees abduction and 5 regained > 50 degrees external rotation starting with the forearm against the chest. To restore hand function ICN was sutured to radial nerve in 40 patients and medial nerve in 10 patients. Motor recovery was poor in both nerve transfers but protective sensation was regained in the	Combination of different nerve transfers.

		fingers innervated by median nerve in 9/10 patients. For PNT: respiratory function at 2 years was within normal range and no problem with daily activities.	
Sungpet A, Suphachatwong C, and Kawinwonggowith V (2000) Restoration of shoulder abduction in brachial plexus injury with phrenic nerve transfer. Australian & New Zealand Journal of Surgery 70 (11): 783–5.	Case series n=10 (mean age 32.8 years) BPI- total root avulsions (10), c5 ,c6 root avulsions (5) Intervention: PNT to SSN (mean time from injury to surgery was 3.8 months). Follow-up: 19.2 months	The average shoulder abduction was 41 degrees. The average degree of shoulder abduction in patients with C5 or C6 root avulsions was slightly more than that in the patients with total root avulsions. There was no clinically significant respiratory insufficiency in any patient.	Larger studies included in table 2.
Siqueira MG and Martins RS (2009) Phrenic nerve transfer in the restoration of elbow flexion in brachial plexus avulsion injuries: how effective and safe is it? Neurosurgery 65 (4:Suppl): 31.	Case series n=14 (mean age 24.8 years) Patients with complete palsy of the upper limb. PNT to MCN with nerve graft. Mean interval from injury to surgery =6 months Follow-up: average 3.4 years	70% (7/10) patients recovered functional level biceps strength (MRC grade>3). All patients exhibited a transient decrease in pulmonary function tests but without clinical respiratory problems. No significant differences between the right and left PNT. No major complications related to surgery. All patients persisted with some limitation of diaphragmatic excursion (at least I intercostal space).	Larger studies included in table 2.
Waikakul S, Orapin S, and Vanadurongwan V (1999) Clinical results of contralateral C7 root neurotization to the median nerve in brachial plexus injuries with total root avulsions. Journal of Hand Surgery - British Volume 24 (5): 556–60.	Prospective survey n=96 Patients with BPI (total root avulsions) Intervention: mainly combinations of nerve neurotisations done. Mainly contralateral C7 root to median nerve. Other ones-PN to SSN and SAN to MCN. Follow-up: 3 years	Contralateral C7 neurotisation results: at 3 years most patients had encouraging recovery of sensory function in the hand but motor function of the forearm and hand muscles was rather poor. Acceptable motor function was found in only 50% to 60% of the patients who were younger than 18 years.	Combinations of various nerve neurotisations done. Mainly contralateral C7 root to median nerve. Not clear how many patients had PNT.
Wang S, Yiu HW, Li P et al. (2012) Contralateral C7 nerve root transfer to neurotize the upper trunk via a modified prespinal route in repair of brachial plexus	Case series n=41 (mean age 29.2 years) Patients with BPAI including combined accessory nerve and/or	The functional recovery of shoulder abduction in patients with additional suprascalpular nerve neurotisation was remarkably improved. No complications related	Patients from C5-C8 or C5-T1 nerve root complete avulsion injury combined with an ipsilateral accessory nerve and /or phrenic

avulsion injury. Microsurgery 32 (3): 183–8.	phrenic nerve palsy Intervention: contralateral C7 nerve root transfers using modified prespinal route,The suprascalpular nerve neurotised by PN or terminal motor branch of accessory nerve in some patients. Follow-up: mean 47.2 months	to procedure for creation of the prespinal route.	nerve injury.
Xu J, Cheng X, Dong Z et al. (2001) Remote therapeutic effect of early nerve transposition in treatment of obstetrical brachial plexus palsy. Chinese Journal of Traumatology 4 (1): 40–3.	Case series n=12 Patients with neuroma (8) and rupture or avulsion (4) Intervention: early nerve transposition Follow-up: 40-50 months	Excellent and good recovery in functions was found in 75% of patients and the excellent rate of PN and accessory nerve transposition was 83.3% and 66.7% respectively. A complete recovery in shoulder and elbow joint function was in 3 patients and mallet IV was in 6 patients.	Patients with indications other than BPI were also included in the study.
Xu WD, Lu JZ, Qiu YQ et al. (2008) Hand prehension recovery after brachial plexus avulsion injury by performing a full-length phrenic nerve transfer via endoscopic thoracic surgery. Journal of Neurosurgery 108 (6): 1215–9.	Case series n=3 Patients with complete BPI Intervention: full length PNT to median nerve via endoscopic thoracic surgery Follow-up: 3 years	The power of the palmaris longus, flexor pollicis longus and the flexor digitorum muscles of all 4 fingers reached grade 3-4/5. No symptoms of respiratory insufficiency occurred.	Larger studies included in table 2.
Xu WD, Xu JG and Gu (2005) Comparative clinical study of Vascularised and Nonvascularised full-length phrenic nerve transfer. Microsurgery 25: 16–20.	Comparative case series n=15 patients with BPI Full length PNT (compares 3 procedures: 1. Reserving the initial part of phrenic nerve and dissecting the full-length distal nerve and pulling out from the supraclavicular incision, 2. Retaining the cervical segment and isolating the thoracic segment of the phrenic nerve from the interspace of the second intercostals, pectoralis major and deltoid muscle (subclavicular incision), 3. Vascularised PNT,	7 patients had the procedures on the left side and 8 had on the right side. All 3 procedures had no significant differences ($F< F_{0.005\ (V1,V2)}$, $P > 0.05$) and reported same functional recovery of the biceps muscle at 28 months follow-up.	Very small sample size. No safety data reported. Data from a similar publication included in table 2.

	same as second, except the thoracic phrenic nerve was dissected with the pericardiophrenic vessels and pulled out from the subclavicular incision. Follow-up; 28-35 months		
Yang J, Chen L, Gu Y et al (2011). Selective neurotization of the radial nerve in the axilla using a full-length phrenic nerve to treat complete brachial plexus palsy: an anatomic study and case report. Neurosurgery 68 (6): 1648–53.	Case report n=1 Patient with complete brachial plexus palsy Intervention: full length PNT to radial nerve (other nerve transfers were also done) Follow-up: 3 years	The patient's antebrachial extensor muscles regained Grade 4 power when assessed 3 years after surgery. No complications or respiratory dysfunction occurred postoperatively.	Larger studies included in table 2.
Zhao X, Lao J, Hung LK et al. (2004) Selective neurotization of the median nerve in the arm to treat brachial plexus palsy. An anatomic study and case report. Journal of Bone & Joint Surgery - American Volume 86-A (4): 736–42.	Case report n=1 Patient with complete brachial plexus palsy Intervention: full length PN T to reinnervate the posterior fascicular group of the median nerve (other nerve transfers were also done) Follow-up: 16 months	Muscles supplied by the posterior fascicular group regained grade 4 power (MRC) 16 months after surgery. 3 years after surgery. No complications or respiratory dysfunction occurred postoperatively.	Larger studies included in table 2.
Zheng MX, Xu WD, Qiu YQ et al. (2010) Phrenic nerve transfer for elbow flexion and intercostal nerve transfer for elbow extension. Journal of Hand Surgery - American Volume 35 (8): 1304-9.	Retrospective case series n=7 patients: brachial plexus avulsion injuries Phrenic nerve transferred to the musculocutaneous nerve and intercostal nerves transfer to triceps branch of the radial nerve (nerve transfers done 7 to 12 years ago). Follow-up: retrospective	Functional elbow flexion was obtained in most of the 7 cases. Elbow extension was absent or insufficient in all subjects. Electrical results showed successful biceps reinnervation in 6 patients and successful triceps reinnervation in 5. No patient experienced breathing problems, and pulmonary function results were within normal range.	2 stage nerve transfer, both PNT and ICN transfer, first PNT and then ICN transfer after 2 months. Larger studies included in table 2.
Zhang G, Gu YD et al. (1990) Root avulsion of brachial plexus in infants and children. Chinese Medical Journal 103 (5): 424–7.	Retrospective case series n=21 (children) Patients with root avulsion of brachial plexus Intervention: PNT in early years and transfer of accessory, intercostal	Follow-up of 16 patients showed excellent results in 2 patients, good in 11, fair in 1 and poor in 2. Good results can be obtained if mutli-paired nerve transfer is adopted in treatment. A 5-year-old patient who had concomitant treatment of	Multiple publication Updated study with data on children included in table 2 (Gu YD 1996).

	nerves, motor branches of the cervical plexus and other proximal stump of broken roots was also performed in later years. PNT (N=21). Follow-up: average 3 years 2 months (range 1 to 10 years and 7 months).	PNT and ICN had severe dyspnea, marked elevation of the diaphragm and minimisation of pulmonary volume. Owing to the anatomical and physiological characteristics of the respiratory system in children, it is harmful to perform phrenic nerve transfer concomitantly with intercostal nerve transfer.	

Appendix B: Related NICE guidance for phrenic nerve transfer in brachial plexus injury

There is currently no NICE guidance related to this procedure.

Appendix C: Literature search for phrenic nerve transfer in brachial plexus injury

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	12/12/12	Issue 12 of 12, Dec 2012
Database of Abstracts of Reviews of Effects – DARE (Wiley)	12/12/12	-
HTA database (Wiley)	12/12/12	-
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	12/12/12	Issue 12 of 12, Dec 2012
MEDLINE (Ovid)	12/12/12	1946 to November Week 3 2012
MEDLINE In-Process (Ovid)	12/12/12	December 06, 2012
EMBASE (Ovid)	12/12/12	1974 to 2012 Week 49
CINAHL (NLH Search 2.0 or EBSCOhost)	-	Technical problems reported- results will be included when fixed.

Trial sources searched on

- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov
- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database

Websites searched

- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference search
- Evidence Updates (NHS Evidence)

General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

1	Phrenic Nerve/

2	(phrenic adj3 nerve*).tw.
3	(nervus adj3 phrenicus).tw.
4	or/1-3
5	exp Brachial Plexus/
6	exp Brachial Plexus Neuropathies/
7	(brachial* adj3 plexus).tw.
8	(axillary adj3 plexus).tw.
9	(musculocutaneous adj3 nerve*).tw.
10	(neuralgic adj3 amyotrophy).tw.
11	(brachial adj3 plexopath*).tw.
12	(klumpke* adj3 (palsy or paralys*)).tw.
13	(erb* adj3 (duchenne or paralys* or pals*)).tw.
14	avulsion*.tw.
15	(distal adj3 denervation).tw.
16	or/5-15
17	Nerve Transfer/
18	Nerve Regeneration/
19	(nerve adj3 (transfer* or crossover* or regenerat* or repair or recover* or transplant* or graft* or allotransplant*)).tw.
20	(neur* adj3 regenerat*).tw.
21	neuroregeneration.tw.
22	Neuroti*.tw.
23	(innervation adj3 diaphragm).tw.
24	Reconstructive Surgical Procedures/
25	(reconstruct* adj3 surg*).tw.